

Dated: November 14, 2001.

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Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of Biotechnology Activities; Recombinant DNA Research: Actions Under the NIH Guidelines

AGENCY: National Institutes of Health (NIH), PHS, DHHS.

ACTION: Notice of actions under the NIH Guidelines for research involving recombinant DNA molecules (NIH Guidelines) and request for comment on the information collection provisions under the Paperwork Reduction Act of 1995.

SUMMARY: The actions described in this Notice amend the NIH Guidelines to enhance oversight of human gene transfer research by modifying the requirements for the reporting and analysis of serious adverse events in human gene transfer research studies governed by the NIH Guidelines.

The first action modifies the scope of serious adverse events that are reportable on an expedited basis. Expedited reporting will now be required for those serious adverse events that are unexpected and associated with the use of the gene transfer product (i.e., there is a reasonable possibility that the experience may have been caused by the gene transfer product). The change also provides timeframes for expedited reporting and definitions of serious, associated, and unexpected adverse events. Under the amendments, summary information about other adverse events would be included in annual reports. Principal Investigators with multiple studies may submit a single annual report, provided that data are attributed to discrete sites. The annual reporting requirements are set forth in Appendix M-I-C-3 and the safety reporting requirements are in Appendix M-I-C-4. Those two sections have been submitted for OMB approval under the Paperwork Reduction Act of 1995 and this notice provides 30 days for public comment on those information collection requirements. Following this comment period, OMB analysis of the comments, and approval of the requirements, NIH OBA will publish a notice setting forth the

effective date of Appendices M-I-C-3 and M-I-C-4.

The second action clarifies that, in accordance with applicable law and longstanding policy of the NIH Office of Biotechnology Activities (OBA), when information submitted in serious adverse event reports and annual reports is labeled trade secret or confidential commercial information, the NIH OBA will assess this claim and make a determination. If NIH OBA determines that the data so labeled are confidential commercial or trade secret and that their public disclosure would promote an understanding of key scientific or safety issues, the NIH OBA will seek agreement from the appropriate party to release such data.

The third action adds specific language to the NIH Guidelines to prohibit the submission of individually-identifiable patient information in serious adverse event and annual reports.

The fourth action is the establishment of a working group of the NIH Recombinant DNA Advisory Committee (RAC), to be known as the NIH Gene Transfer Safety Assessment Board (GTSAB), that will play a role in the analysis of safety information in gene transfer research studies. The working group will report safety information to the RAC and, thereby, disseminate it to the scientific and patient communities, as well as the general public.

In toto, these four changes will enhance the identification of significant safety issues across human gene transfer trials, increase public knowledge, and strengthen the protection of research participants in human gene transfer research studies. These changes are an important step toward harmonization of Federal safety reporting requirements. Additional efforts are underway within the Department of Health and Human Services to further enhance consistency in the collection of safety information and submission of safety reports, increase the quality of safety reports, and expedite review of critical safety information. NIH will continue to monitor and participate in these efforts, reevaluating and, as appropriate, changing the NIH Guidelines.

DATES: Comments on the information collection requirements in Appendix M-I-C-3 and Appendix M-I-C-4 must be submitted to the OMB at the address shown below by December 19, 2001. As information collection requirements, Appendix M-I-C-3 and Appendix M-I-C-4 will take effect upon OMB approval. All other provisions will take effect 30 days after November 19, 2001.

ADDRESSES: Comments should be sent to: Office of Information and Regulatory Affairs, Office of Management and Budget, New Executive Office Bldg., 725 17th Street, NW., Room 10235, Washington, DC 20503, Attn: Desk Officer for NIH.

FOR FURTHER INFORMATION: Background documentation and additional information can be obtained from the Office of Biotechnology Activities, National Institutes of Health, MSC 7985, 6705 Rockledge Drive, Suite 750, Bethesda, Maryland 20892, Phone 301-496-9838, FAX 301-496-9839. The NIH OBA Web site is located at <http://www4.od.nih.gov/oba/>

SUPPLEMENTARY INFORMATION:

I. Background

This Action follows from a Proposed Action published in the December 12, 2000 **Federal Register** (65 FR 77655) and derives from an extensive process of deliberation and public consultation. It takes into account the reports of two specially convened NIH working groups as well as numerous written comments from the public on two separate proposals. The preponderant view emerging from this process supports the four main objectives of this Action, which are to: (1) Harmonize NIH requirements for expedited reporting of serious adverse events in gene transfer trials with those of FDA; (2) clarify how claims that annual and safety reports contain confidential commercial or trade secret information will be resolved, given the need for disclosure of information to ensure broad public knowledge of issues raised by gene transfer research; (3) maintain the privacy of individuals participating in gene transfer research; and (4) develop a new mechanism for the analysis and dissemination of adverse event information with the goal of enhancing knowledge about scientific and safety trends. The history leading up to each element of this Action is discussed below.

A. Scope and Timing of Serious Adverse Event Reports

A major purpose of this Action is to harmonize NIH requirements for the reporting of serious adverse events with those of the FDA. This harmonization is expected to enhance compliance with the NIH Guidelines. Significant non-compliance with the NIH Guidelines became evident in 1999 following the death of a participant in a human gene transfer research study. Subsequent to this event, the NIH OBA called on investigators conducting these studies to submit to the Office comprehensive pre-

clinical and clinical data. In the course of gathering and assessing this data, the NIH OBA discovered that serious adverse events were not being reported as required by the NIH Guidelines. Concerted efforts were immediately initiated to enhance awareness of, and compliance with, the reporting requirements. To that end, NIH proposed that the NIH Guidelines be amended to make the requirements for reporting serious adverse events more explicit.

The proposed amendments, adding specific definitions and timeframes for the expedited reporting of serious adverse events, were first published for public comment in the November 22, 1999, **Federal Register** (64 FR 63827). The proposal clarified existing NIH policy, which required that all serious adverse events occurring in conjunction with human gene transfer trials be reported immediately to the NIH OBA, the IBC, the IRB, and, if applicable, the Office for Human Research Protections. This requirement applied whether or not the event was expected or deemed to be associated with the gene transfer product. FDA, on the other hand, requires expedited reporting of only those serious adverse events that are unexpected and associated with the gene transfer product (i.e., there is a reasonable possibility that the experience may have been caused by the gene transfer product). Unlike the NIH requirement, the FDA rules (21 CFR 312.32) provide specific timeframes for reporting these events. Since most investigators are subject to both the NIH Guidelines and FDA regulations, and full compliance is essential to federal oversight of gene transfer research, greater uniformity is an important objective.

The Advisory Committee to the Director, NIH (ACD) formed a working group in early December 1999 to review NIH's role in the oversight of human gene transfer studies, including serious adverse event reporting. The ACD working group recommended that the NIH and FDA work together to simplify, streamline, and harmonize reporting of serious adverse events. In June 2000, the RAC reviewed the conclusions and recommendations of the ACD Working Group and, after engaging in further discussion about the appropriate timing and scope of serious adverse event reporting, endorsed the ACD Working Group recommendations by a unanimous vote. In September 2000, the full ACD reviewed and adopted the recommendations of the working group at a publicly accessible teleconference.

These ACD recommendations, RAC endorsement of the recommendations,

and public commentary all culminated in the Proposed Action of December 12, 2000. The proposal called for reporting unexpected serious adverse events possibly associated with the gene transfer product to the NIH OBA within 15 days after sponsor notification, or within 7 days if such an event were also fatal or life-threatening.

B. Analysis of Serious Adverse Events

The ACD Working Group also reaffirmed the need for the NIH OBA to gather cumulative safety data on gene transfer trials. They noted that systematic analyses of adverse event data would improve the conduct and safety of such research by revealing trends related to, for example, specific diseases, routes of administration, or vectors.

Public deliberations of the ACD and the RAC emphasized the importance of NIH's role in ensuring the safety of human gene transfer research studies. The NIH studies scientific and safety trends in gene transfer research and disseminates that information to investigators. This role in important ways complements the regulatory responsibility of the FDA, which includes assessing the overall safety of individual gene transfer products used in multiple trials and assessing the safety of broader classes of gene transfer products sharing related vectors. The NIH and FDA share the goal of developing a body of knowledge about the science and outcomes of this form of clinical investigation.

In this regard, the ACD recommended creation of a standing expert body that would review all reports of adverse events, analyze the data for trends, develop a cumulative report that would be presented annually at a public RAC meeting and made available to the public, and identify trends or even single events that may warrant further public discussion or federal action. They suggested that this standing body should include basic scientists, clinicians, patient advocates, and ethicists, and that ad hoc members should be appointed to provide additional expertise on an as-needed basis.

Thus, as part of the December 12, 2000 **Federal Register** notice, the NIH proposed the establishment of a new working group of the RAC, called the NIH Gene Transfer Safety Assessment Board (GTSAB). The GTSAB's specific functions were proposed to involve: (1) Reviewing in closed session serious adverse event reports, annual reports, and other relevant safety information and assessing toxicity and safety data across gene transfer trials and analyzing

the data for trends; (2) identifying significant trends or single events; and (3) reporting aggregated data to the RAC. This Board is expected to enhance review of new protocols and public understanding and awareness of the safety of human gene transfer research studies as well as inform the decision-making of potential trial participants.

C. Confidentiality of Adverse Event and Annual Reports and Patient Privacy

In September 1999, the RAC initiated discussions regarding public access to serious adverse event information. This discussion was in response to several serious adverse event reports submitted to the NIH OBA which were labeled as confidential. The NIH has always acknowledged and affirmed the need to protect trade secret and other proprietary information, such as the details of a sponsor's manufacturing process. This principle is accommodated in the NIH Guidelines. The concept that serious adverse events per se should be considered from a commercial standpoint as confidential, however, is contrary to NIH's longstanding commitment to public access to information about the safety of human gene transfer research. NIH has always sought to ensure public access to safety information and, in Appendix M-I-B-2, actively discourages the labeling of information submitted in accordance with Appendix M as confidential. In instances where data have been properly labeled as confidential commercial or trade secret, NIH has acknowledged that claim, in accordance with applicable law, and sought agreement for any proposed public disclosure of that data. Nonetheless, the NIH Guidelines were not explicit about the confidentiality of serious adverse event reports, and thus the NIH OBA asked the RAC to consider whether the NIH Guidelines should be modified to clarify the requirement for public access to these reports. In response, the RAC concurred that adverse event data are essential to decision-making by IBCs, IRBs, and potential subjects of gene transfer research in humans. The RAC added that the public disclosure of adverse events is essential to public understanding and evaluation of gene transfer in humans.

The December 12, 2000 proposal elaborated on existing language on this topic by stating that adverse event and annual reports would not be considered confidential commercial information. In this Action, this statement has been revised in accordance with existing law to provide for case-by-case resolution of claims that adverse event or annual reports contain confidential commercial

information. This statement has also been repositioned within Appendix M of the NIH Guidelines to enhance its salience and clarity.

Finally, the proposal reinforced a longstanding tenet that in submitting adverse event reports, investigators should take measures to protect the privacy of patients and their families.

II. Summary

The amendments that emerged from this extensive process of public deliberation were published for public comment in the December 12, 2000 **Federal Register**. The specific changes proposed to the NIH Guidelines were as follows: (1) Change the requirements for expedited reporting of serious adverse events; (2) clarify that trade secret or other commercial confidential information should not be included in serious adverse event and annual reports and that those reports would not be classified by the NIH OBA as confidential information; (3) add a new section prohibiting individually identifiable patient information from being included in serious adverse event reports; and (4) establish a working group of the RAC, to be known as the NIH Gene Transfer Safety Assessment Board, to be responsible for the review and analysis of serious adverse events and other relevant safety information in gene transfer research studies and dissemination of safety information to the RAC, and, thereby, to the scientific and patient communities, and the public. The deadline for public comment was February 10, 2001.

III. Public Comments

A total of 28 comments were received on the proposal by the deadline, and another ten were received subsequently, for a total of 38. These comments, in the form of letters and e-mails, reflected the views of patients, industry, academic officials, an ethicist, scientists, a law firm, and the public at large. All comments have been reviewed by NIH staff, as well as members of the RAC, who considered the substance and scope of public comments in open session on March 8, 2001.

A. Overview of Comments

All commenters supported the principle of harmonizing requirements with FDA. The majority of comments were supportive of the proposal as written and urged its adoption. These came from associations representing patients, an ethicist, academic officials responsible for biosafety and human subjects oversight, a law firm, and a number of individuals expressing no particular affiliation. A scientific society

representing researchers working on gene transfer techniques also expressed support for the proposal, though it made a number of suggestions for modifying specific components.

Opposition to the proposal was expressed by two industry trade associations, four companies, and two patient groups. These letters expressed a view that the NIH OBA and the RAC should not receive raw data on serious adverse events under any circumstances.

Taken together, objections can be categorized under four thematic headings: (1) Concern about public dissemination of confidential commercial and trade secret information; (2) assertions that such reporting was a duplication of effort, given existing FDA reporting requirements; (3) objections to the perceived regulatory stance on the part of NIH; and (4) challenges to the scope of adverse events reportable in an expedited manner. These are discussed below.

B. Responses to Specific Comments

Comment: The Proposed Action will cause inappropriate release to the public of confidential commercial and trade secret information. These comments suggested that many of the data items specified for inclusion in annual and serious adverse event reports had inherent commercial value, because they could conceivably allow others to infer information about the staging of the clinical trial, the bioavailability of the product, the dose response profile of the intervention, and other matters that would allow competitors to gain advantage in the design of their own trials.

Response: It has been a longstanding and widely accepted tenet of the NIH's 25-year-old system of oversight of recombinant DNA research conducted at NIH-funded institutions that the public dissemination of safety data is key to protecting public health and assuring the public that problems are being identified and addressed in a timely way. The RAC has been receiving and publicly reviewing safety data in gene transfer studies for over a decade. The NIH OBA, in fact, has provided a suggested reporting format that industry has used for a number of years (which can be viewed at <http://www4.od.nih.gov/oba/rac/SAEForm.rtf>). NIH has always acknowledged and affirmed the need to protect trade secret and other proprietary information, such as the details of a sponsor's manufacturing process, and this principle is accommodated in the NIH Guidelines.

Since the current version of the NIH Guidelines is not explicit about the specific content of serious adverse event reports, the Action lists specific data elements that should be reported to the NIH OBA (found in proposed M-I-C-4-a). Before developing this list, NIH OBA staff asked the RAC to consider whether the NIH Guidelines should include such clarifications and be modified to make clear that these data would be publicly accessible. In response, the RAC issued in September 1999 the aforementioned consensus statement that expressed unambiguously that adverse event reports must not be designated as confidential, either in whole or in part, given their importance to decision-making by IBCs, IRBs, and potential research subjects. The Proposed Action elaborated on the RAC recommendation by providing that the NIH OBA would not consider adverse event and annual reports to be confidential commercial information.

The NIH OBA uses this information to issue periodic scientific reports as well as analyses of safety data. When such information is labeled as confidential, the Action clarifies the NIH OBA policy for assessing, in accordance with applicable laws, whether the data are indeed confidential commercial information. In making this assessment, the NIH must carefully consider the views of the owner of the information on the competitive harm that could be caused by disclosure of the labeled information. As necessary, the NIH OBA will seek agreement from the appropriate party to release that information for the purposes of ensuring broad public knowledge of issues raised by gene transfer research. NIH will not publicly disclose information that it determines, under applicable law, to be confidential commercial without the agreement of the owner of that information. This policy is reflected in a new Appendix M-I-C-5 to clarify that it applies to any information submitted under Appendix M-I-C.

Comment: It should suffice to send raw adverse event information to the FDA only under its investigational new drug (IND) application process; submission to the NIH OBA for analysis by the Gene Transfer Safety Assessment Board (GTSAB) represents an unnecessary burden and duplication of effort. These commenters expressed the view that FDA has the scientific expertise, experience, and mechanisms in place to monitor adverse events effectively and in real-time, and has the authority to take action as appropriate to protect research participants. They also valued the broad confidentiality protections that the FDA process offers,

which are not consistent with NIH OBA's mission of disseminating information to patients, scientists, and other members of the public. Some companies suggested that a system might be set up to allow FDA to aggregate, synthesize, and analyze the data before delivering a report to the RAC, which would then look at the gross-level safety trends. Several letters pointed to a concurrent proposal by the FDA (January 18, 2001; 66 Federal Register 4688) to amend the biologics regulations to make available for public disclosure certain data and information related to human gene therapy and xenotransplantation. Given that FDA would be making similar kinds of information routinely available, these commenters questioned why the NIH should duplicate this role.

Response: The GTSAB will have a purpose that is different, though complementary to that of the FDA and other review groups, such as data safety and monitoring boards (DSMBs). The FDA provides immediate responses to reports of safety problems in the context of specific trials. The FDA has the authority to put those trials on hold to allow a full assessment of risks, shield research participants from any potential harm, and preclude the exposure of potential participants to the risks of the trials. In addition, the FDA assesses the overall safety of individual gene transfer products used in multiple trials and assesses the safety of classes of gene transfer products such as products using similar vectors. DSMBs are usually used to review data from a single trial at regular intervals; trials using DSMBs are usually in Phase III. The GTSAB would meet quarterly and conduct macro and longitudinal analyses of data accumulated across gene transfer trials to address questions that will allow the field of gene transfer research to advance safely.

The comprehensive public review of aggregated serious adverse event data by the RAC (through the GTSAB) has been endorsed by the ACD, the RAC, and members of the public as a critical component of the system of federal oversight of human gene transfer research. NIH and FDA will have a broad view of scientific and safety trends in gene transfer research and have the goal of advancement of knowledge in this area. The GTSAB will enhance the public dissemination of information about gene transfer research. A systematic and publicly accountable review and assessment of toxicity and safety data from these trials over time is essential for identifying trends and recognizing patterns that may have important implications for the

future development of human gene transfer research. The GTSAB will augment the NIH's ability to perform this critical function, in accordance with the recommendations of the ACD and in keeping with the agency's responsibility to enhance the science, safety, and ethics of research conducted under the auspices of the NIH Guidelines. NIH and FDA will continue to work closely together in analyzing gene transfer adverse events and will involve the GTSAB as appropriate.

FDA's information disclosure regulations limit that agency's ability to share confidential information regarding gene transfer research with the NIH for the purpose of public disclosure, just as they limit FDA's ability to make such information available directly to the public. Thus, under current FDA regulations, NIH OBA cannot rely on disclosures from the FDA to achieve the objective of public disclosure of the scientific and safety issues. As observed by some commenters, the FDA has a proposal pending to disclose publicly specific categories of data from human gene therapy and xenotransplantation trials. At such time as this proposal is implemented, NIH will reassess and may, as appropriate, change the processes and mechanisms for gathering safety information as outlined in this action. If any future changes in FDA regulations alter reporting requirements so that they are no longer harmonized with the NIH Guidelines, the NIH will modify the NIH Guidelines as appropriate.

The RAC and a majority of public commenters favored the GTSAB, citing the unique role and purpose it will serve. For all of the above reasons, and because of the majority view expressed in public commentary, the GTSAB will be retained.

Comment: In requiring annual reporting and collecting severe adverse event data, the NIH is acting in an inappropriately regulatory manner. This comment suggested that the NIH Guidelines have "mushroomed" into an elaborate, burdensome set of rules, departing from their intended role as "guidance."

Response: The applicability of the NIH Guidelines has remained relatively constant since their inception in 1976, and there has been little change in safety reporting requirements since the 1985 version, which first described reporting policies for human gene transfer activities. Thus, the notion that the NIH Guidelines have expanded into an elaborate set of regulations is unfounded. To the contrary, this Action harmonizes the NIH safety reporting requirements with those of the FDA and

entails an approximately 90 percent reduction in events that investigators will have to report to the NIH OBA on an expedited basis. NIH is offering flexibility in how this requirement is met. The NIH OBA has historically accepted adverse event reports on the FDA MedWatch form to minimize the burden on investigators. Investigators may also choose to use the NIH reporting format, which is based on the MedWatch form with certain reporting items tailored to the context of gene transfer research. Under these amendments to the NIH Guidelines, both formats will continue to be acceptable reporting mechanisms, provided reports are complete with regard to the information specified under new M-I-C-4-a.

In further harmonization with FDA, the NIH has modified the annual reporting requirement to allow investigators with multiple studies to submit a single annual report, provided that data are attributed to discrete sites. To facilitate compliance further, language has been added to explicitly allow the investigator to delegate the reporting task to the sponsor. The ultimate accountability for whether reporting occurs, however, rests with the investigator. Both changes reflect the fact that the NIH's oversight relationship is with institutions and investigators, as reflected historically in NIH Guidelines.

While NIH is not a regulatory agency, it does place conditions upon the funds that it awards to institutions. One of those conditions is compliance with the NIH Guidelines (see 42 CFR 52.8). Thus, the NIH Guidelines apply directly to biotechnology companies only if they receive funding from the NIH for recombinant DNA research. Most biotechnology companies do not receive such funding. Biotechnology companies that are not direct recipients of NIH funding for recombinant DNA research may be affected by the NIH Guidelines, nonetheless. When a company conducts recombinant DNA research in collaboration with an institution that receives any NIH funding for recombinant DNA research, all recombinant DNA research conducted at or sponsored by that institution is subject to the NIH Guidelines. Thus, the industry-sponsored recombinant DNA research conducted at that institution is subject to the reporting requirements addressed in this notice. In addition, a company may voluntarily choose to comply with the NIH Guidelines in accordance with Section IV-D, Voluntary Compliance. Many companies have chosen such voluntary compliance, including compliance with the safety reporting requirements.

Comment: The scope of serious adverse events (related and unexpected) that would have to be reported on an expedited basis is too narrow. In support of this view, commenters expressed concern that the significance of serious adverse events might not be readily discernable, and thus all such events should be reportable on an expedited basis. Comments also expressed the viewpoint that sponsors and scientists may not be objective in making determinations of “relatedness” or “expectedness.”

Response: The NIH OBA agrees that complete reporting of adverse event data is important. Events that may not seem to be of generalizable concern may have implications for the field that are not fully appreciated until they are aggregated and analyzed. Therefore, the NIH OBA will continue to collect summary information about other adverse events in annual reports to this office.

It is important to note that the criteria of “relatedness” and “expectedness” are harmonized with the reporting requirements of the FDA to enhance compliance with expedited reporting of serious adverse events. The goal of harmonization has been considered and supported vigorously by the RAC, the ACD, and a diverse and broad-based public constituency. To employ the broad scope of promptly reportable events that was suggested in some comments would be equivalent to retaining the current requirements and would run counter to the harmonization objective.

Although this change will depend on investigators to make determinations of “relatedness” and “expectedness,” secondary oversight will occur through clinical monitoring plans that NIH and FDA require for clinical trials. Furthermore, it is anticipated that harmonization will enhance compliance with the expedited reporting of those events for which expedited reporting is likely to be of value and, overall, will improve the availability of safety and scientific information for analysis. Consequently, this Action retains the proposed scope of serious adverse events that are reportable on an expedited basis.

IV. RAC Discussion

The Recombinant DNA Advisory Committee (RAC) received copies of all comment letters, as well as synopses of each letter, and an analysis of the commentary in the aggregate. At its March 8, 2001 meeting the RAC reviewed these materials and heard oral commentary by members of the public. The RAC deliberated extensively on the merits of these various arguments and perspectives, and each member individually summarized his or her stance on the proposal. RAC perspectives were overwhelmingly in favor of adopting the Proposed Action, as reflected by a vote of 12 in favor, none opposed, and one abstention.

V. Paperwork Reduction Act of 1995

This Action contains information collections that are subject to review by the Office of Management and Budget

(OMB) under the Paperwork Reduction Act (PRA) of 1995 (44 U.S.C. 3507(d)), and have been submitted for OMB approval as a modification of OMB Control No. 0925-0001. A description of the information collection provisions and an estimate of the annual reporting burden are provided below.

Title: Annual reporting.

Description: The annual reporting provisions in Appendix M-I-C-3 would clarify the specific information items that investigators would have to report to NIH OBA within 60 days after the one-year anniversary of the date on which the investigational new drug (IND) application was filed with the FDA, and after each subsequent anniversary until the trial is completed. Appendix M-I-C-3 reduces the reporting burden by providing that, when multiple studies are conducted under the single IND, the Principal Investigator (or delegate) may choose to submit a single annual report covering all studies, provided that each study is identified by its OBA protocol number. Table 1 depicts the estimated reporting burden of complying with this aspect of the proposal. The estimated burden has been calculated by multiplying the approximate number of open protocols presently (since there is one report per protocol) by the number of hours typically required to prepare each report.

Description of Respondents:

Investigators conducting human gene transfer research.

TABLE 1

NIH guidelines for research involving recombinant DNA molecules	Total number of reports annually (based on one report per open protocol)	Hours to prepare each report	Total hours
Appendix M-I-C-3	200	4	800

Title: Serious adverse event reporting.
Description: Under Appendix M-I-C-4, expedited reporting will be required for those serious adverse events that are unexpected and associated with the use of the gene transfer product (i.e., there is a reasonable possibility that the experience may have been caused by the gene transfer product). Appendix M-I-C-4 provides that these reports must be

made as soon as possible, but not later than 15 calendar days after the sponsor’s initial receipt of the information, or 7 days if the event is fatal or life-threatening. Table 2 provides an estimate of the total reporting burden based on the number of reports NIH expects to receive (per past experience). The burden is calculated by estimating the number of

event that will be reportable on an expedited basis (by culling events that fit this classification out of the total reports received by OBA) and multiplying them by the time it takes to fill out an FDA MedWatch form or the NIH OBA reporting format.

Description of Respondents:

Investigators conducting human gene transfer research.

TABLE 2

NIH guidelines for research involving recombinant DNA molecules	Number of serious adverse events reported annually that are unexpected and related	Hours to prepare each response	Total hours
Appendix M-I-C-4	120	1	120

These information collection requirements are intended to reduce the burden of reporting important safety data to the NIH by harmonizing the reporting requirements with those of FDA, limiting data elements to those necessary for NIH to identify significant safety issues in human gene transfer trials, and providing a reasonable timeframe for submission of the reports.

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995, the agency has submitted the information collection provisions of this Action to OMB for review. Interested persons are requested to send comments regarding information by December 19, 2001 to Office of Information and Regulatory Affairs, Office of Management and Budget, New Executive Office Bldg., 725 17th Street, NW., Room 10235, Washington, DC 20503, Attn: Desk Officer for NIH. Upon OMB approval, NIH OBA will publish a notice setting forth the effective date of these requirements.

Amendments to the NIH Guidelines

Pursuant to the rationale expressed above and the recommendations of the NIH RAC, the ACD, and the majority of public commentary, the NIH Guidelines are amended as follows:

A New Section I-E-8 Is Added To Read

“Section I-E-8. A ‘serious adverse event’ is any event occurring at any dose that results in any of the following outcomes: death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization also may be considered a serious adverse event when, upon the basis of appropriate medical judgment, they may jeopardize the human gene transfer research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.”

A New Section I-E-9 Is Added To Read

“Section I-E-9. An adverse event is ‘associated with the use of a gene transfer product,’ when there is a reasonable possibility that the event may have been caused by the use of that product.”

A New Section I-E-10 Is Added To Read

“Section I-E-10. An unexpected serious adverse event is any serious adverse event for which the specificity or severity is not consistent with the

risk information available in the current investigator’s brochure.”

Section IV-B-7. Principal Investigator (PI) Is Modified To Read

“Section IV-B-7. Principal Investigator (PI)

On behalf of the institution, the Principal Investigator is responsible for full compliance with the NIH Guidelines in the conduct of recombinant DNA research. A Principal Investigator engaged in human gene transfer research may delegate to another party, such as a corporate sponsor, the reporting functions set forth in Appendix M, with written notification to the NIH OBA of the delegation and of the name(s), address, telephone, and fax numbers of the contact. The Principal Investigator is responsible for ensuring that the reporting requirements are fulfilled and will be held accountable for any reporting lapses.”

Current M-I-C-3, Annual Reporting, Is Modified in Its Entirety To Read

“Appendix M-I-C-3. Annual Reports

Within 60 days after the one-year anniversary of the date on which the investigational new drug (IND) application was filed with the FDA, and after each subsequent anniversary until the trial is completed, the Principal Investigator (or delegate) shall submit the information set forth in (a), (b), and (c). When multiple studies are conducted under the single IND, the Principal Investigator (or delegate) may choose to submit a single annual report covering all studies, provided that each study is identified by its OBA protocol number.

(a) Clinical Trial Information. A brief summary of the status of each trial in progress and each trial completed during the previous year. The summary is required to include the following information for each trial: (1) The title and purpose of the trial; (2) clinical site; (3) the Principal Investigator; (4) clinical protocol identifiers, including the NIH OBA protocol number, NIH grant number(s) (if applicable), and the FDA IND application number; (5) participant population (such as disease indication and general age group, e.g., adult or pediatric); (6) the total number of participants planned for inclusion in the trial; the number entered into the trial to date; the number whose participation in the trial was completed; and the number who dropped out of the trial with a brief description of the reasons; (7) the status of the trial, e.g., open to patient accrual, closed but data collection ongoing, or fully completed,

and (8) if the trial has been completed, a brief description of any study results.

(b) Progress Report and Data Analysis. Information obtained during the previous year’s clinical and non-clinical investigations, including: (1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system; (2) a summary of all serious adverse events submitted during the past year; (3) a summary of serious adverse events that were expected or considered to have causes not associated with the use of the gene transfer product such as disease progression or concurrent medications; (4) if any deaths have occurred, the number of participants who died during participation in the investigation and causes of death; and (5) a brief description of any information obtained that is pertinent to an understanding of the gene transfer product’s actions, including, for example, information about dose-response, information from controlled trials, and information about bioavailability.

(c) A copy of the updated clinical protocol including a technical and non-technical abstract.”

Current Appendix M-I-C-4, Serious Adverse Event Reporting, Is Modified in Its Entirety To Read

“Appendix M-I-C-4. Safety Reporting

Principal Investigators must submit, in accordance with this section, Appendix M-I-C-4-a and Appendix M-I-C-4-b, a written report on: (1) Any serious adverse event that is both unexpected and associated with the use of the gene transfer product (i.e., there is reasonable possibility that the event may have been caused by the use of the product; investigators should not await definitive proof of association before reporting such events); and (2) any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity. The report must be clearly labeled as a “Safety Report” and must be submitted to the NIH Office of Biotechnology Activities (NIH OBA) and to the local Institutional Biosafety Committee within the timeframes set forth in Appendix M-I-C-4-b.

Principal Investigators should adhere to any other serious adverse event reporting requirements in accordance with federal regulations, state laws, and local institutional policies and procedures, as applicable.

Principal Investigators may delegate to another party, such as a corporate sponsor, the reporting functions set forth in Appendix M, with written

notification to the NIH OBA of the delegation and of the name(s), address, telephone and fax numbers of the contact(s). The Principal Investigator is responsible for ensuring that the reporting requirements are fulfilled and will be held accountable for any reporting lapses.

The three alternative mechanisms for reporting serious adverse events to the NIH OBA are: by e-mail to oba@od.nih.gov; by fax to 301-496-9839; or by mail to the Office of Biotechnology Activities, National Institutes of Health, MSC 7985, 6705 Rockledge Drive, Suite 750, Bethesda, Maryland 20892.

Appendix M-I-C-4-a. Safety Reporting: Content and Format

The serious adverse event report must include, but need not be limited to: (1) The date of the event; (2) designation of the report as an initial report or a follow-up report, identification of all safety reports previously filed for the clinical protocol concerning a similar adverse event, and an analysis of the significance of the adverse event in light of previous similar reports; (3) clinical site; (4) the Principal Investigator; (5) NIH Protocol number; (6) FDA's Investigational New Drug (IND) Application number; (7) vector type, e.g., adenovirus; (8) vector subtype, e.g., type 5, relevant deletions; (9) gene delivery method, e.g., in vivo, ex vivo transduction; (10) route of administration, e.g., intratumoral, intravenous; (11) dosing schedule; (12) a complete description of the event; (13) relevant clinical observations; (14) relevant clinical history; (15) relevant tests that were or are planned to be conducted; (16) date of any treatment of the event; and (17) the suspected cause of the event. These items may be reported by using the recommended Adverse Event Reporting Format available on NIH OBA's web site at: <http://www4.od.nih.gov/oba/>, the FDA MedWatch forms, or other means provided that all of the above elements are specifically included.

Reports from laboratory animal studies as delineated in Appendix M-I-C-4 must be submitted in a narrative format.

Appendix M-I-C-4-b. Safety Reporting: Time-frames for Expedited Reports

Any serious adverse event that is fatal or life-threatening, that is unexpected, and associated with the use of the gene transfer product must be reported to the NIH OBA as soon as possible, but not later than 7 calendar days after the sponsor's initial receipt of the

information (i.e., at the same time the event must be reported to the FDA).

Serious adverse events that are unexpected and associated with the use of the gene transfer product, but are not fatal or life-threatening, must be reported to the NIH OBA as soon as possible, but not later than 15 calendar days after the sponsor's initial receipt of the information (i.e., at the same time the event must be reported to the FDA).

Changes in this schedule are permitted only where, under the FDA IND regulations [21 CFR 312(c)(3)], changes in this reporting schedule have been approved by the FDA and are reflected in the protocol.

If, after further evaluation, an adverse event initially considered not to be associated with the use of the gene transfer product is subsequently determined to be associated, then the event must be reported to the NIH OBA within 15 days of the determination.

Relevant additional clinical and laboratory data may become available following the initial serious adverse event report. Any follow-up information relevant to a serious adverse event must be reported within 15 calendar days of the sponsor's receipt of the information. If a serious adverse event occurs after the end of a clinical trial and is determined to be associated with the use of the gene transfer product, that event shall be reported to the NIH OBA within 15 calendar days of the determination.

Any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity must be reported as soon as possible, but not later than 15 calendar days after the sponsor's initial receipt of the information (i.e., at the same time the event must be reported to the FDA)."

A New Appendix M-I-C-5 Is Added To Read

"Appendix M-I-C-5. Confidentiality

Data submitted in accordance with Appendix M-I-C that are claimed to be confidential commercial or trade secret information must be clearly labeled as such. Prior to making its determination about the confidentiality of data labeled confidential commercial or trade secret, the NIH will contact the Principal Investigator or delegate to ascertain the basis for the claim and subsequently will notify the Principal Investigator or delegate of its final determination regarding the claim.

If NIH determines that the data so labeled are confidential commercial or trade secret and that their public

disclosure would promote an understanding of key scientific or safety issues, the NIH will seek agreement from the appropriate party to release such data. Public discussion of scientific and safety issues raised by data submitted in accordance with Appendix M-I-C is vital to informing both investigators and patients about the safety of gene transfer research.

To protect the privacy of participants in gene transfer research, any serious adverse event or annual reports submitted to NIH OBA must not contain individually identifiable patient information."

A New Appendix M-I-D Is Added To Read

Appendix M-I-D. Safety Assessment in Human Gene Transfer Research

A working group of the RAC, the NIH Gene Transfer Safety Assessment Board, with staff support from the NIH OBA, will: (1) Review in closed session as appropriate safety information from gene transfer trials for the purpose of assessing toxicity and safety data across gene transfer trials; (2) identify significant trends or significant single events; and (3) report significant findings and aggregated trend data to the RAC. It is expected that this process will enhance review of new protocols, improve the development, design, and conduct of human gene transfer trials, promote public understanding and awareness of the safety of human gene transfer research studies, and inform the decision-making of potential trial participants."

Current Appendix M-IV. Privacy and Confidentiality Is Modified To Read

"Appendix M-IV. Privacy

Indicate what measures will be taken to protect the privacy of patients and their families as well as maintain the confidentiality of research data. These measures should help protect the confidentiality of information that could directly or indirectly identify study participants."

* * * * *

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally, NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers virtually every NIH and federal research program in which recombinant DNA techniques could be used, it has been

determined not to be cost effective or in the public interest to attempt to list these programs. In addition, NIH could not be certain that every federal program would be included as many federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

Dated: October 19, 2001.

Ruth L. Kirschstein,

Acting Director, National Institutes of Health.

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BILLING CODE 4140-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Substance Abuse and Mental Health Services Administration

Agency Information Collection Activities: Proposed Collection; Comment Request

In compliance with section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995 concerning opportunity for public comment on proposed collections of information, the Substance Abuse and Mental Health Services Administration will publish periodic summaries of proposed projects. To request more information on the proposed projects or to obtain a copy of the information collection plans, call the SAMHSA Reports Clearance Officer on (301) 443-7978.

Comments are invited on: (a) Whether the proposed collections of information are necessary for the proper performance of the functions of the agency, including whether the information shall have practical utility; (b) the accuracy of the agency's estimate of the burden of the proposed collection

of information; (c) ways to enhance the quality, utility, and clarity of the information to be collected; and (d) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques or other forms of information technology.

Proposed Project: Methamphetamine Abuse Treatment—Special Studies (MAT-SS)

New—The Methamphetamine Abuse Treatment—Special Studies (MAT-SS) project is a family of coordinated studies funded by SAMHSA's Center for Substance Abuse Treatment (CSAT) that will serve as a follow-up to the CSAT Methamphetamine Treatment Project (MTP). The MTP was conducted to compare the outcomes of the Matrix Model of methamphetamine treatment with Treatment-as-Usual in and across multiple treatment sites, and to assess the feasibility and outcomes generated by a technology transfer of the Matrix Model. Participants included 150 methamphetamine dependent clients recruited at each treatment site who were randomly assigned to one of the treatment conditions. Participants, diverse in demographic characteristics, and in individual and environmental circumstances, were evaluated at admission, weekly during treatment, at discharge, and at 6 and 12 months after treatment admission. Participating treatment sites include eight programs in seven geographical areas: Billings, Montana; Honolulu, Hawaii; and Concord, Costa Mesa, San Diego, Hayward, and San Mateo, California.

The family of studies included in the MAT-S project will address diverse issues associated with the phenomena of methamphetamine dependence. The Multi-Year Methamphetamine Treatment Follow-up Study will assess the long-term outcome and functioning of individuals who previously participated in treatment for methamphetamine dependence. The study will utilize a 36-month post-

intake, face-to-face, one-on-one structured interview. Multiple measures typically utilized in substance abuse research with established psychometric properties will be employed to assess the longitudinal course of methamphetamine dependence and its consequences. A randomly selected sample of follow-up participants will also be interviewed to collect medical, neurological, and psychiatric data. The Adherence to Manualized Treatment Protocols Over Time Study will assess issues associated with the adoption of the Matrix Model of treatment and/or Matrix treatment components after the formal MTP study period has ended, specifically addressing adherence to the manualized treatment protocol. Interviews of both staff and clients will utilize a semi-structured, face-to-face format. Finally, The Cost Analysis of Outpatient Methamphetamine Treatment Study will evaluate the cost effectiveness of both the Matrix and Treatment-as-Usual treatment conditions in each treatment site. Two data collection methods will be utilized and to collect information from both administrator interviews and review of administrative and financial records.

The conceptual underpinning of the MAT-SS project is a recognition by SAMHSA and leading experts in the field that escalating methamphetamine abuse nationwide necessitates a longitudinally focused investigation addressing the process, nature, and consequences of methamphetamine dependence. The overall goals of the MAT-SS project are to document the longitudinal process of addiction and recovery in methamphetamine-dependent individuals, ascertain the feasibility and success of implementing a manualized treatment protocol in community-based treatment settings, and evaluate the cost effectiveness of various treatments for methamphetamine dependence. The following table summarizes the burden for this project.

	Number of respondents	Responses per respondent	Hours per response	Total burden hours
Follow-up client interviews	1,016	1	3.0	3,048
Follow-up interviews/exams	508	1	2	1,016
Treatment adherence interviews	144	2	1.5	432
Cost analysis interviews	20	2	1.5	50
Cost analysis document review	8	2	6	96
Total	1,188			4,642
Annual average	396			1,547

Send comments to Nancy Pearce, SAMHSA Reports Clearance Officer,

Room 16-105, Parklawn Building, 5600 Fishers Lane, Rockville, MD 20857.

Written comments should be received within 60 days of this notice.