Attachment D

Technology Innovation Program

Guidelines and Documentation Requirements for Research Involving Human and Animal Subjects

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NIST
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A. Introduction

If any project participants, collaborators, or contractors propose involving people as software or device testers, using human blood or tissue samples, or collecting data or biological materials from living individuals then the regulations involving human subjects in research most likely apply. Read this kit for guidance on the required documentation for proposals and ongoing awards.

The Technology Innovation Program (TIP or "the Program") will fund research involving human subjects. Research involving human subjects must comply with all applicable federal statutes, Executive Orders, federal regulations, and policies. Applicable authorities are listed in Appendix 1.

For research involving human subjects, the National Institute of Standards and Technology (NIST) requires NIST as an institution to review and approve required documentation following the review and recommendation for approval by the Program. Research activities involving human subjects are not authorized to start within an award until approval for each specific activity by a specific performer is issued in writing from the NIST Grants Officer. The Federal Policy for the Protection of Human Subjects (the Common Rule), adopted by the Department of Commerce (DOC) at 15 C.F.R. Part 27, sets forth the applicable policies and procedures for the protection of human subjects in research. The Common Rule adopted by the Department of Commerce is available at http://www.access.gpo.gov/nara/cfr/waisidx_99/15cfr27_99.html.

The Common Rule defines the term *research* as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (see Section P Definitions). Any proposal funded by the Program is considered to be research, and subject to this definition.

The Common Rule defines *human subject* as a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information (see Section P Definitions). The Common Rule provides a systematic means, based on established, internationally recognized ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities. An awardee institution bears the responsibility for safeguarding the rights and welfare of human subjects in DOC-supported research.

The term "research involving human subjects" is broad and covers many types of applications, some of which may not be obvious to someone with limited or no experience with the applicable regulations. It encompasses the study and observation of human behavior, reactions, and thought processes as well as the study of the human body, tissues, organs, and cells. The use of any human subjects in a research project must be evaluated. For example, human testing of computer software, observation of human reactions or actions in specified settings, investigation of human cells or tissue, and in certain circumstances even completion of surveys by study volunteers or employees may fall within the scope of research involving human subjects.

To determine if human subjects are involved in your research project, complete Appendix 2, Human Subjects Determination Checklist. A research project may contain multiple activities in which human subjects are involved. The checklist should be used to evaluate each distinct activity and potential use of human subjects. For instance, a project may involve software testing by a subject population with a subsequent collection of user attitudes about the software through a questionnaire. Software performance testing is potentially one use of human subjects, while completion of a questionnaire is potentially a distinct second use of human subjects. Both activities need to be analyzed separately using the checklist to determine whether human

subjects are involved in the research project. The checklist will then indicate whether an exemption to 15 C.F.R. Part 27 may be appropriate (see section B), or whether there may be no involvement of human subjects in the specific research activity.

Every proposer must consider the following aspects carefully: why human subjects are needed on the proposed project, what is the minimum needed involvement of human subjects, and the anticipated risk to the subjects. If a proposer can restructure the use of human subjects in the project with minimal impact on the research in order to minimize risk of harm and/or eliminate uses of identifiable private information, it will likely be beneficial to the human subjects review.

B. Research Exempt from the Regulations

Certain research activities may qualify for an exemption from the requirements of the Common Rule. Uses of human subjects that are exempt from the regulations still require review and approval in advance by NIST before the activities may begin. The categories of research that qualify for an exemption can be found at 15 C.F.R. 27.101(b). The types of exemptions that may typically be requested for NIST to review for applicability include but are not limited to the following:

- Research conducted in established or commonly accepted educational settings, involving normal educational practices such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness or of the comparison among instructional techniques, curricula, or classroom management methods. [15 C.F.R. 27.101(b)(1)]

- Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects, and (ii) any disclosure of the human subjects' responses outside the research could reasonably place subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. [15 C.F.R. 27.101(b)(2)]

- Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. [15 C.F.R. 27.101(b)(4)]

For research activities that may be considered exempt, the proposer or current award recipient must complete Appendix 3 or Appendix 4 as appropriate, and provide the Appendix to the Program with the proposal or to the project manager with sufficient time for the Program's evaluation of the request for current projects. If you believe a research activity is exempt, the exemption number you indicate on the SF-424 in "Research & Related Other Project Information" will be evaluated to determine if an exemption is appropriate for the intended research. If appropriate, the relevant documents will be generated to recommend approval of the exemption by the NIST Grants Office. Once the NIST Grants Officer approves the specific request for exempt research, no subsequent review is required as long as the exempted research activity does not change. If there are research activity changes from what was originally approved, a request to re-review the research activity using Appendix 3 or Appendix 4 to determine whether or not an exemption still applies is required.

Exemptions are not available for research involving the protected class identified at 45 C.F.R. 46 Subpart C (prisoners). Also, the exemption at 15 C.F.R. 27.101(b)(2) for research involving survey or interview procedures or observation of public behavior does not apply to research with children, except for research involving observations of public behavior when the investigator or

investigators do not participate in the activities being observed.

Appendices 3 and 4 are described below to assist you in requesting an exemption from the requirements of 15 C.F.R. Part 27:

Appendix 3: Request for an Exemption from 15 C.F.R. Part 27 for Research Involving Human Subjects in Information Technology, Manufacturing, or Imaging Studies will assist you in determining if a research activity in any of these areas may be exempt. The principal investigator must answer all questions, sign, date, and submit the completed questionnaire to the Program for review and determination of whether the research activity is exempt or not considered a use of human subjects in research under the regulations. The answers to these questions are used by the Program to prepare the appropriate recommendation to the NIST Grants Officer for the research activity. If additional data or materials not previously approved are to be added to the project, an additional Appendix 3 or 4 must be submitted.

Appendix 4: Request for an Exemption from 15 C.F.R. Part 27 for Research Involving Human Subjects Involving Biological Studies will assist you in determining if a research activity requiring the purchase or use of live human tissues, human cells, or human-derived cell lines may be exempt. The principal investigator must answer all questions, sign, date, and submit the completed questionnaire to the Program for review and determination of whether the research activity is exempt or not considered a use of human subjects in research under the regulations. The answers to these questions are used by the Program to prepare the appropriate recommendation to the NIST Grants Officer for the research activity. If additional data or materials not previously approved are to be added to the project, an additional Appendix 3 or 4 must be submitted.

Some organizations require Institutional Review Board (IRB) approval of exemption requests. If your organization uses an IRB to approve exemptions, documentation from the IRB of that approval, which clearly notes the exemption, is a required attachment to Appendices 3 and 4. Unless required by your organization, an IRB approval is not required by NIST to evaluate a research activity as exempt.

C. Non-Exempt Research Involving Human Subjects

If it is determined that human subjects are involved in a research activity and that an exemption does not apply, the research activity will require review by an Institutional Review Board (IRB) registered with the Office of Human Research Protections (OHRP) within the Department of Health and Human Services (DHHS) (http://www.hhs.gov/ohrp/). The IRB must be designated as a cognizant IRB on the Federalwide Assurance (FWA) of each organization engaged in the research activity involving human subjects (see Section E Assurance of Compliance). If the principal investigator and/or any collaborators conducting the research activity providing results to the project will have access to private information linked to an individual or identifiers that could link data or specimens to an individual, that research activity may require IRB review, followed by a NIST administrative review and recommendation for approval to the NIST Grants Officer before the research activity may be initiated. Retroactive approvals are not permitted.

Concerns may be identified during the NIST administrative review that could require a subsequent review and re-approval by the cognizant IRB. Please read ***Appendix 7: Common Documentation Issues*** carefully when preparing documentation for IRB review to help you avoid issues which may delay final NIST approval of your request.

For initial proposals, if you expect to require an IRB review for a research activity in the first year, you may be asked for additional information during the review by the Evaluation Panel. For example,

you may be asked to submit any documentation that may have already obtained IRB approval since the proposal was submitted (i.e., the research activity protocol, consent forms, recruitment materials – ads and screening scripts, etc.). If IRB approval has been obtained before the proposal is submitted, a copy of the IRB approval memo and all associated documentation should be attached (See Chapter 1 Section F). For research activities involving human subjects that will be submitted to an IRB for review only if an award is issued, the Program may ask for clarification(s) of these research activities during the Evaluation Panel's review of the proposal.

For ongoing projects, submission to NIST of a draft of all documentation that will require IRB review (i.e., the research activity protocol, consent forms, recruitment materials – ads and screening scripts, etc.) in advance of submission to the cognizant IRB is an option that is strongly encouraged to help minimize iterations through the cognizant IRB.

The Health Insurance Portability and Accountability Act (HIPAA), at 45 C.F.R. Parts 160 and 164, regulates the use of identifiable health information from individuals by covered entities. HIPAA requires that individuals be notified about their privacy rights and how their information will be used or disclosed and that permission, known as an Authorization, be obtained prior to use of the information. It also requires the adoption of internal privacy policies and procedures and training of individuals to assure that the privacy of identifiable data is maintained. Covered entities include health plans, health care clearinghouses, and health care providers. Not all researchers will have to comply with the HIPAA rules. However, a researcher who is a health care provider, or who works for a health care provider (as a covered hospital, or health plan), or who will be using or accessing data from medical or patient records and/or databases will need to comply with the rules as implemented by the cognizant HIPAA covered entity. Consultation about HIPAA rules and their application to specific situations from the HIPAA covered entity will aid the researcher in the quest to use health data and will assist covered entities in meeting the HIPAA requirements. Most HIPAA covered entities can assist you with determining the requirements of their organization, and most IRBs can direct you to the appropriate contact in their organizations if you have questions about HIPAA compliance and how it may impact your proposed research task.

Every proposer must consider carefully why human subjects are needed for the proposed research activity in either a new proposal or an ongoing project, what the minimum needed involvement of human subjects is, and the anticipated risk to the subjects. If a proposer can restructure the use of human subjects in the project with minimal impact on the research in order to minimize risk of harm and/or eliminate uses of identifiable private information, it may speed the NIST administrative review.

D. Engagement in Human Subjects Research

An organization is considered to be "engaged" in human subjects research if it or its agents intervene or interact with living individuals for research purposes or obtain private information (e.g., medical records) about an individual that can be linked to that individual. Primary award recipient institutions are considered to be engaged in human subject research whenever they receive funding for an award that includes such research. The primary award recipient bears ultimate responsibility for protecting human subjects under the award. Examples of organizations engaged in human subjects research include:

- The organization or its agents intervene with living individuals by performing invasive or noninvasive procedures. (i.e., draw blood, test physical therapy devices, or test the user interface on a piece of software).
- The organization or its agents intervene with living individuals by manipulating the environment: light, sound, temperature, orchestrate social interactions, make voice, digital, or image recordings (i.e., test a biometric device).

- The organization or its agents intervene with living individuals in protocol-dictated communications, research interviews, or survey questionnaires. Obtaining informed consent for a research activity is considered interaction with a subject.
- The organization or its agents obtain individually identifiable private information about human subjects (e.g., health records).
- The primary organization receiving an award, which includes human subjects research activities, even if the human subjects research activity will be conducted by a joint venture participant, subcontractor or direct collaborator associated with the award.

There are numerous conditions under which an organization may be considered engaged in a research activity involving human subjects. **Please contact the TIP Human and Animal Subjects Advisor if you have any questions about engagement in human subjects research by any of the project participants.**

E. Assurance of Compliance

The primary applicant organization proposing to include human subjects in non-exempt research must have a written assurance approved for federalwide use (a Federalwide Assurance – FWA) on file with the Office for Human Research Protections (OHRP) within the Department of Health and Human Services (DHHS) before the research is submitted for IRB review. The Common Rule at section 27.103(a) requires that each institution "engaged" in federally supported human subject research file an assurance of compliance with the requirements of the Common Rule.

An assurance formalizes the institution's commitment to protect human subjects and formally commits the institution to oversight by a specific OHRP-registered IRB. Under the Common Rule at section 27.102(f), awardees and their collaborating institutions become engaged in human subjects research whenever their employees or agents (1) obtain data through intervention or interaction with living individuals for research purposes or (2) obtain individually identifiable private information for research purposes.

The primary award recipient is also responsible for ensuring that each joint venture partner, subcontractor, and formal collaborating institution that is engaged in human subjects research has an approved Federalwide Assurance (FWA) on file with OHRP.

The Program only accepts a current Federalwide Assurance (FWA), also referred to as the "Human Subject Assurance number" on the SF-424. Information regarding how to apply for an FWA from OHRP can be found at http://www.hhs.gov/ohrp/assurances/assurances_index.html.

F. Required Documentation

The proposer is required to indicate on the Application for Federal Assistance Form SF-424 (R&R) and the Research & Related Other Project Information forms whether the project involves exempt and/or non-exempt human subjects research activities. If the project does involve human subjects, the proposer will indicate under Item 1.a.:

1. if the IRB review is pending,

2. the IRB approval date (if currently approved for exempt or non-exempt research),

3. a proposed or IRB-approved exemption number (if research is exempt), and

4. the human subject Federalwide Assurance (FWA) number for the primary applicant organization should be provided, or indicate "applied for," if non-exempt human subjects activities are proposed at any time within the project. If more than the primary applicant organization is involved in non-exempt human subjects research in the first year, the FWA numbers for each engaged institution should be included within the portion of the technical plan that addresses the use of human subjects. If any FWAs are being applied for, that should also be indicated within the technical plan. FWA information for subcontractors can be provided or as part of the NIST-1022B item 4.

NIST and the Program reserve the right to make an independent determination of whether your research involves human subjects. If NIST or the Program determines that your research project involves human subjects, you will be required to provide additional information for review and approval. A timeline for the submission of required documents can be found in Appendix 5.

1. Non-Exempt Human Subjects Research Beginning During Year 1 of a Proposal or Within the Current Year of an Award.

For review and approval of non-exempt research planned in the first year of a proposed project or the current year of an award, copies of all documents submitted to and approvals received from the IRB(s) overseeing the research must be submitted to the Program if an award is issued. The Program may request information regarding the status of the following documentation for studies proposed in Year 1 of a project proposal during review of proposals by the Evaluation Panel or to clarify issues during the internal NIST review for funded projects.

Since IRB approvals are for one-year periods only, the same documentation requirements apply to IRB re-approvals, and must be approved by NIST before the research is continued. This documentation requirement also applies to any IRB-approved amendments to the research. Required documentation includes the following:

a. the name of the institution(s) where research will be conducted, the IRB name(s) (including the institutional name) and IRB registration numbers of the IRB(s) that will have oversight, and the Federalwide Assurance (FWA) number(s) on file with OHRP for *all of the organizations* engaged in the planned research activity linked to the cognizant IRB(s);

b. a signed (by the study principal investigator) copy of the final Institutional Review Board (IRB)-approved human subjects research protocol for each of the specific research tasks;

c. a copy of all IRB-approved consent forms, interview scripts and subject recruiting materials (i.e., e-mail text, advertisements, posters etc.);

d. a signed and dated approval letter from the cognizant IRB(s) that includes the name of the institution housing each applicable IRB, and provides the start and end dates for the approval of the research;

e. any IRB-required interim reporting or continuing review requirements;

f. a copy of any IRB-required application information, such as documentation of approval of special clearances (i.e., biohazard, HIPAA, etc.), conflict-of-interest letters, or special training requirements;

g. a brief description of what portions of the protocol are specifically included in the proposal or ongoing project, if the protocol includes tasks not applicable to the proposal or ongoing project, or if the protocol is supported by multiple funding sources. For protocols with multiple funding sources, NIST will not approve the study without a nonduplication-of-funding letter indicating that no other federal funds will be used to support the tasks proposed under the proposed research or ongoing project;

h. any additional clarifying documentation that NIST may request during review of proposals by the Evaluation Panel or to perform the internal NIST review for funded projects.

If any organizations use an electronic approval process without paper-based signatures by the PI or IRB for any of the above documentation, please consult with either the TIP Human & Animal Subjects Advisor or the project manager.

The protocol, consent forms, interview scripts and recruitment materials should bear the notation used by the IRB to indicate that those exact document versions are the ones reviewed and approved by the IRB.

NIST will review all of this documentation. Frequently problems with the documentation are found during this review and require changes and re-approval by the IRB or IRB(s) involved. Please read carefully Appendix 7: Common Documentation Issues when preparing documentation for IRB review to help you avoid issues which delay final NIST approval of your request. If you expect to require an IRB review for a research activity in the first year of your proposed research, you have the option, and are encouraged after official notification that an award has been issued to submit a draft of the research activity protocol associated with the project in advance of IRB review to help minimize iterations through the cognizant IRB.

2. Exempt Human Subjects Research Beginning During Year 1 of a Proposal or Within the Current Year of an Award.

If the involvement of human subjects in the research plan may qualify for an exemption from the Common Rule, a completed exemption request form (Appendix 3 and/or 4) for each activity involving human subjects, as applicable, must be submitted to the Program with your proposal submission or to the project manager for current projects when requested. If needed, include Appendix 3 and/or Appendix 4 as part of the consolidated file to be attached to the Research and Related Other Project Information form (see Chapter 5 of the TIP Proposal Preparation Kit). The Program may request additional documentation during review of proposals by the Evaluation Panel or to perform the internal NIST review for funded projects.

a. ***Appendix 3: Request for an Exemption from 15 C.F.R. Part 27 for Research Involving Human Subjects in Information Technology, Manufacturing, or Imaging Studies*** is required if a research activity in any of these areas may be exempt. The principal investigator must answer all questions, sign, date, and submit the completed questionnaire to the Program for review and determination of whether the research activity is exempt or not considered a use of human subjects in research under the regulations.

b. ***Appendix 4: Request for an Exemption from 15 C.F.R. Part 27 for Research Involving Human Subjects Involving Biological Studies*** is required if a research activity requires the purchase or use of live human tissues, human cells, or human-derived cell lines and may be exempt. In addition, the use of materials which are not custom collected may be considered a nonuse of human subjects in the research and not subject to human subject regulations. Even if you believe that your situation may be a nonuse of human subjects, submission of Appendix 4 is required. The use of custom collected materials typically requires IRB review of the project. The principal investigator must answer all questions, sign and date and submit the completed questionnaire to the Program for review and determination of whether the research activity is exempt or not considered a use of human subjects in research under the regulations.

3. Exempt or Non-Exempt Human Subjects Research Beginning After Year 1 of a Proposal or Proposed for a Later Year in a Current Project.

If there are no research tasks involving human subjects in the first year of the proposal or the current year of an award, but there are tasks anticipated beyond the first or current year, a

detailed request for a deferred IRB approval and/or a deferred exemption request as appropriate under 15 C.F.R. 27.118 must be submitted to the Program with your proposal submission or to the project manager for current projects when requested. The Program may request additional documentation during review of proposals by the Evaluation Panel or to perform the internal NIST review for funded projects.

A deferral request **must** include the following information:

a. An outline of the tasks that will be performed using human subjects.

b. The projected start date for the use of human subjects (e.g., second quarter of year 3).

c. An outline of when the required documentation, as outlined above in sections F.1 and F.2, will be submitted to the Program for review and NIST approval.

d. If the research will require IRB review and approval, an outline of current plans for:

   i. the name of the institution(s) where the research will be conducted,

   ii. the name(s) and registration numbers of the IRB(s) that will have oversight, the name of the institution(s) housing the IRB(s) and

   iii. the Federalwide Assurance (FWA) number(s) on file with OHRP for all of the organizations engaged in the planned research activity linked to the cognizant IRB(s).

   iv. If FWAs need to be obtained for any organizations, the expected date to file for all FWAs that will be required.

G. Guidance for Developing Consent Forms

Obtaining informed consent from human volunteers in research studies is subject to the requirements outlined in 15 C.F.R. 27.116 and the rules for documentation of the process as described in 15 C.F.R. 27.117. Obtaining informed consent is a process, not just a subject's signature on a piece of paper. The process is designed to show respect for subjects who desire to make a voluntary act of participating in a research study. The process educates the potential subject in a way that enables the subject to understand the risks associated with their participation and how to seek assistance if they have questions about the study, or if they believe they have been harmed during the study. The consent form should be written in the language(s) and at the level(s) consistent with the average educational ability anticipated for the target subject group(s). This may require translation into another language to ensure comprehension. The consent document may require revision during a study if new information becomes available that could impact the subjects' understanding of the elements of personal risk and use of private information, and possibly alter their decision about continuing participation. The consent form must be consistent with the final Institutional Review Board (IRB)-approved human subjects research protocol. Deviations in the consent form from the protocol will require revision of the consent form and/or the protocol and re-approval by the cognizant IRB.

NIST requires that each consent form include a statement that OHRP, NIST, and other federal officials, as appropriate, have the right to inspect study records if deemed necessary.

The OHRP provides tips and a checklist on what to include in a consent form to meet the regulatory requirements:

Consent form tips:
http://www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm

Consent form checklist: http://www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm

A summary of the OHRP resources for consent forms is provided below; key issues for Program proposals, as well as ongoing projects, are specifically noted:

- A statement that the study involves research should be incorporated at the beginning of the form.
- The consent form should contain an explanation of the purposes of the research and any relevance it might hold for the study subject.
- A description of the proposed study population, including inclusion and exclusion criteria which may be used to select subjects.
- A description of the procedures to be used during the study should be given, specifically noting which procedures are experimental. The activities undertaken by both the research subjects and the investigators should be described. Also, the amount of time required of the subject should be given.
- A description of any anticipated risks or discomforts that may occur during the study should be described, as well as the possibility that other, unforeseen risks may occur.
- A description of any benefits that the subject could reasonably anticipate gaining from participation in the study should be given. (Note: Compensation is not a benefit. Compensation is discussed in a separate section.).
- If applicable, any other alternative non-experimental procedures that could reasonably be expected to be of benefit to the subject instead of the new, experimental procedure should be described.
- A description is required of how confidentiality will be maintained during and after the study, including how long data will be retained and how it will be destroyed if that is the intent. What happens to the data in the event of a subject's withdrawal should be explained. HIPAA requirements may apply to the study data and should be examined. **NIST requires that a statement be included that OHRP, NIST, and other federal officials as appropriate have the right to inspect study records if deemed necessary.**
- A description of any compensation to be offered for participation should be provided including when and how it will be paid (e.g., cash immediately after the session or a check 6-8 weeks after participation). This section must also explain how the compensation is affected should the subject withdraw from the study.
- What treatments/procedures are available for any injury that might occur during the study should be explained. This section must also include the name, study position, and phone number of the person(s) the participant should contact in the event of a research-related injury. The term "injury" must be used in designating this contact.
- **NIST requires two contact names in the consent form:** 1) the name of who to contact if the research subjects have questions about the research that arise before or during the study, and 2) the name of who to contact if there are questions about the subject's rights as a subject in research. The term "questions" must be used in identifying these contact people.
- A statement should be provided that participation is voluntary and the subject may withdraw at any time during the study. This should also include a statement that refusal to participate or withdrawal during the study will not result in the loss of any benefits to which the subject is otherwise entitled.
- The withdrawal process should be clearly stated and easy to follow, with well-defined procedures for 1) how withdrawal impacts data collected up to receipt of the withdrawal notification from the subject and 2) payments due or not due to the subject for incomplete participation.

The consent may include additional items, such as circumstances under which the investigator may un-enroll a subject, any additional costs to the subject that may occur during the study, or that research results will be given to the subject. The subject must be given sufficient time to read and understand the consent form prior to being expected to sign the form. In addition, the subject should have an opportunity to ask questions about the consent form and the study. The subject should also be given a copy of the final signed consent for future reference.

H. Protected Classes

Research involving pregnant women, human fetuses, neonates, prisoners, or children must comply with 45 C.F.R. 46 Subparts B, C, or D, respectively. The DHHS regulations describe additional protections required for these human subjects. NIST considers all custom collection of human gestational tissues (e.g., yolk sac) or cells to be covered by subpart B. The regulations for research involving the protected classes identified in subparts B, C, and D can be found at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

The use of prisoners requires that the IRB overseeing this research include a prisoner or prisoner representative. Very few IRBs typically meet this requirement, but IRBs may add members to meet this requirement. However, ***the Program reserves the right not to fund a research task involving prisoners as human subjects***, and during the review of a proposal by the Evaluation Panel the proposer may be asked to describe the technical impact on the project if that activity is removed from the project.

IRB approval memos for research activities involving protected classes should contain a clear statement acknowledging the involvement of protected classes and that the IRB review specifically addressed the review requirements for approving such research.

I. Research Involving Human Subjects in Information Technology, Manufacturing, or Non-Clinical Imaging Studies

Small scale human testing of computer software, observation of human reactions or actions in specified settings (i.e., on a manufacturing floor, or by security cameras) and in certain circumstances even completion of surveys by study volunteers or employees may fall within the scope of research involving human subjects.

To determine if human subjects are involved in your research project, complete Appendix 2, Human Subjects Determination Checklist. A research project may contain multiple activities in which human subjects are involved. The checklist should be used to evaluate each distinct activity and potential use of human subjects. For instance, a project may involve software testing by a subject population with a subsequent collection of user attitudes about the software through a questionnaire. Small scale software performance testing is potentially one use of human subjects, while completion of a questionnaire is potentially a distinct second use of human subjects. Each activity must be analyzed using the checklist to determine whether human subjects are involved in the research project. The checklist will then indicate whether the possibility that an exemption to 15 C.F.R. Part 27 is appropriate, or if there is no involvement of human subjects.

NIST reserves the right to make an independent determination of whether your research involves human subjects. If NIST determines that your research project involves human subjects, you will be required to provide additional information for review and approval. A timeline for the submission of required documents can be found in Appendix 5.

Every proposer must consider carefully the following: why human subjects are needed in the proposed project, the minimum needed involvement of human subjects, and the anticipated risk to the subjects. If a proposer can restructure the use of human subjects in the project with minimal impact on the research in order to minimize risk of harm and/or eliminate uses of identifiable private information, it will likely be beneficial to the human subjects review.

Some studies involving large numbers of human subjects, may be considered to be either product development, or pre-commercial-scale demonstrations where the emphasis is on demonstrating that some technology works on a large scale or is economically sound rather than on R&D that extends the state of the art. These types of studies are ineligible for Program funding (TIP 2008 Proposal Preparation Kit Chapter 1 Section D Ineligible Projects and Ineligible Costs).

J. Clinical Trials

On a case-by-case basis, the Program may partially support research as part of a Phase I clinical trial. The Program expects requests to support Phase I clinical trials to be rare, and it is highly unlikely that this type of trial could be fully funded within a project. If the proposed research includes all or any portion of a Phase I clinical trial, the research must be deemed consistent with all applicable Program scientific and technological award criteria requirements. However, ***the Program reserves the right not to fund a Phase I clinical trial.*** During proposal review by the Evaluation Panel the proposer may be asked to describe the technical impact on the project if that activity is removed from the project.

Costs associated with a Phase II, Phase III, or Phase IV clinical trial are ineligible for Program funding.

K. Human Subjects in Foreign Countries

Generally, the Program does not fund research involving human subjects in foreign countries. The Program will consider, however, the use of **preexisting** tissue, cells, or data from a foreign source on a limited basis if the following criteria are satisfied:

1. the scientific source is considered unique,
2. an equivalent source is unavailable within the United States,
3. an alternative approach is not scientifically of equivalent merit, and
4. the specific use qualifies for an exemption from the Common Rule.

If the above information does not sufficiently address a particular situation involving foreign countries, please call the TIP Human & Animal Subjects Advisor for further assistance.

L. Fetuses and Transplantation of Fetal Tissue

Research involving human fetuses must meet all of the requirements set forth at section 498(b) of the Public Health Service Act, 42 U.S.C. §§ 289g. Research involving the transplantation of human fetal tissue into human subjects must be carried out in accordance with the requirements of Section 111 of the NIH Revitalization Act of 1993, 42 U.S.C. § 289g-1 http://www.hhs.gov/ohrp/humansubjects/guidance/publiclaw103-43.htm. Guidance from OHRP can be found at http://www.hhs.gov/ohrp/humansubjects/guidance/fetal.html.

M. Embryos and Embryonic Stem Cells

The NIST Technology Innovation Program adheres to all Presidential policies, statutes, guidelines, and regulations regarding the use of human embryos and human embryonic stem cells. Based on the current direction provided for the use of federal funds for research involving human embryo and embryonic stem cell research, the Program will not consider new proposals or activities in ongoing awards that involve the use of human embryos or human embryonic stem cells.

If new direction is provided on the use of federal funds involving human embryo and human embryonic stem cell research, the Program will not consider new proposals or activities in ongoing awards that involve the use of human embryos or embryonic stem cells until NIST has had the opportunity to fully assess such direction and develop implementation procedures through appropriate approval requirements, and NIST has publicly announced those procedures.

N. Cadaveric Materials

The use of cadaveric materials is governed by applicable state and local laws and is not directly regulated by the Common Rule. The Program still requires that Appendix 4 be filled out for the use of cadaveric materials to document usage and sources.

O. Contact Information

If you have any questions regarding the use of human subjects in research, please call the TIP Human and Animal Subjects Advisor at 301–975–8779. The information contained in this booklet is also available on the TIP website at http://www.nist.gov/tip/helpful.htm**.**

P. Definitions

Terms used in this booklet are defined in the Common Rule at 15 C.F.R. Part 27 or in the National Institutes of Health SF-424 grant application.

The regulations under 15 C.F.R. Part 27 can be found at http://www.access.gpo.gov/nara/cfr/waisidx_99/15cfr27_99.html.

Clinical Trial: A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Custom Collection: The collection or gathering of organs, tissues, cells, or data for the purpose of research that would have otherwise not been collected or gathered.

Human Subject: A living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information. [15 C.F.R. 27.102(f)]

The regulations governing human subjects extend to the use of human organs, tissues, cells, and bodily fluids from individually identifiable human subjects as well as to graphic, written, or recorded information derived from individually identifiable human subjects.

Individually Identifiable Private Information: Private information or specimens are considered to be individually identifiable when they can be linked to a specific individual by the investigator(s) directly or indirectly with or without a coding system. Information which cannot be linked to an individual directly or indirectly is not considered individually identifiable.

Intervention: Includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. [15 C.F.R. 27.102(f)]

Phase I Clinical Trial: A clinical trial done to test a new biomedical or behavioral intervention in a small group of people (e.g., 20–80) for the first time to evaluate safety, efficacy, and effectiveness (e.g., determine a safe dosage range and identify side effects).

Phase II Clinical Trial: A clinical trial study of the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.

Phase III Clinical Trial: A clinical trial study to investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

Phase IV Clinical Trial: A clinical trial study that is conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

Prisoner: Is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Private Information: Includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. [15 C.F.R. 27.102(f)]

Research: A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. [15 C.F.R. 27.102(d)]

II. Research Involving Live Vertebrate Animals

A. Introduction

If your project involves live vertebrate animals as research subjects in a task performed by a project participant, collaborator, or contractor, then the regulations involving animal subjects in research most likely apply. Read this kit for guidance on the required documentation for proposals and ongoing awards.

The Technology Innovation Program (TIP, or the Program) will fund research involving live vertebrate animals. Research involving live vertebrate animals must be in compliance with all applicable federal statutes, federal regulations, and policies. For research involving live vertebrate animals, NIST procedures require that NIST as an institution review and approve documentation in addition to the Program's review and recommendation for approval.

NIST and the Program follow the requirements of the Animal Welfare Act at 7 U.S.C. §§ 2131–2159. In addition, the cognizant Institutional Animal Care and Use Committee (IACUC) should follow the recommendations in the National Research Council's *Guide for the Care and Use of Laboratory Animals* (the *Guide*) as a basis for developing and implementing an institutional animal care and use program. These policies do not affect applicable state or local laws or regulations that may impose more stringent standards for the care and use of laboratory animals.

The requirements described below do not apply to proposed research using preexisting images of animals (e.g., a wildlife documentary or pictures of animals in newscasts) or to research plans that do not include live vertebrate animals that are being cared for, euthanized, or used by the project participants to accomplish research goals, teaching, or testing. These requirements also *do not* apply to obtaining animal materials from commercial processors of animal products or to animal cell lines or tissues from tissue banks.

Q. Institutional Animal Care and Use Committee (IACUC) Review and Compliance

NIST and the Program require that the IACUC that reviews and approves the care and use of live vertebrate animals maintain and comply with appropriate institutional assurances, certifications, or accreditations.

Depending on the research and type of live vertebrate animal involved in the research, NIST and the Program require that the cognizant IACUC maintain *at least one* of the following:

1. documentation of an Animal Welfare Assurance from the Office of Laboratory Animal Welfare (OLAW) of the Public Health Service/National Institutes of Health (PHS/NIH); or

2. documentation of a United States Department of Agriculture (USDA) Animal Welfare Act certification; or

3. evidence of full accreditation from the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC), if only using rodents, birds, or fish, and the above USDA or OLAW documents have not been obtained.

R. Animal Study Protocols

NIST and the Program require that each use of live vertebrate animals be reviewed and approved through the use of an Animal Study Protocol (ASP). The ASP must be completed and signed by the study Principal Investigator or designee and reviewed and approved by the IACUC where the animals will be housed, cared for, and manipulated before any research is started.

NIST and the Program recommend that an approved ASP include the elements suggested by OLAW. These elements can be found online at http://grants.nih.gov/grants/olaw/olaw.htm#assur. A sample ASP is also available from OLAW: http://grants.nih.gov/grants/olaw/sampledoc/animal_study_prop.htm.

During the review by the Evaluation Panel, draft ASPs may be requested for animal studies in the first year of the proposed project. Final approved ASPs will be required if the proposal is funded. For ongoing projects, either the approved ASP or a draft of a proposed ASP for animal studies can be included with the request for initial review of the study. If a draft is initially submitted, a final IACUC-approved ASP will be required for NIST final review and approval before initiation of the animal study. An example of an ASP or an ASP of a different study that is somewhat similar to what may eventually be submitted to an IACUC for review is not acceptable for final NIST review and approval.

Also, if the ASP includes tasks not applicable to the approved scope of the project, or if the ASP is supported by multiple funding sources, a brief description of what portions of the ASP are specifically included in the project is required. For ASPs that involve multiple funding sources, a nonduplication-of-funding letter indicating that no other funds will be used to support the tasks proposed for Program funding must be submitted before NIST will approve the ASP to begin in an ongoing project or in a proposal selected for funding.

S. Required Documentation

You are required to indicate on the Application for Federal Assistance Form SF-424 (R&R) and the Research & Related Other Project Information forms whether or not your research plan will involve the use of live vertebrate animals. If it does, you will indicate the following:

1. if the IACUC review is pending,

2. the IACUC approval date (if currently approved),

3. the assurance number for the cognizant IACUC, as appropriate.

   If more than one IACUC is involved in approving research involving live vertebrate animals in the first year, the assurance type for each IACUC and the IACUC's institution should be included within the technical plan discussion of those animal studies, or as part of the NIST 1022B item 4 for subcontractors performing animal studies.

   a. For AAALAC assurances – indicate "AAALAC".

   b. For OLAW assurances – indicate the OLAW assurance number, i.e. A-1234.

   c. For USDA Animal Welfare Act certification – indicate the certification number, i.e., 12-R-3456.

The documentation requirements for the use of live vertebrate animals in funded projects are listed below. In addition, a timeline for the submission of required documents is presented in

Appendix 6. During review of your proposal by the Evaluation Panel, you may be asked to provide clarifications regarding the proposed use of live vertebrate animals such as how the use of live vertebrate animals in research relates to the proposed technical plan, the qualifications of the proposed institution where the animal research will be carried out, and the timetable to obtain required IACUC approval. To help you avoid issues which may delay final NIST approval of your request, please read ***Appendix 7: Common Documentation Issues*** carefully when preparing documentation for IACUC review.

1. Live Vertebrate Animal Research Beginning During Year 1 of a Proposal or Within the Current Year of an Ongoing Project.

If your research proposal includes plans to use live vertebrate animals in the first year, the following will be required if the proposal is funded or in the current project year for an ongoing project.:

a. the name of the institution(s) where the animals will be housed and where the animal research will be carried out, the name(s) of the IACUC(s) at those institutions that will have oversight; and the type of institutional assurance (OLAW), certification (USDA), or accreditation (AAALAC) held by the institution(s);

b. a signed (by the study Principal Investigator) copy of the IACUC-approved ASP;

c. documentation of the IACUC approval indicating the approval and expiration dates of the ASP (NOTE: Documentation of IACUC approval must include the signature of the authorized approval authority, typically the chairperson of the IACUC or their official designee. Letters signed by IACUC coordinators or personnel other than the IACUC approval authority are not acceptable.); and

d. if applicable, a nonduplication-of-funding letter.

2. Live Vertebrate Animal Research Beginning After Year 1 of a Proposal or Proposed for a Later Year in an Ongoing Project.

If your research proposal includes the use of live vertebrate animals beginning after year 1, the following documentation will be required if the proposal is funded or when first requested for an ongoing project:

a. the name of the organization(s) that may be performing the animal studies;

b. an indication of whether the organization conducting the research and whose IACUC will approve the research has an appropriate OLAW Animal Welfare Assurance, USDA certification, or AAALAC accreditation; and

c. a timeline for the use of live vertebrate animals, including an approximate date for IACUC approval and when the approved ASP and related materials will be submitted to NIST for review.

Before live vertebrate animal research studies may begin, the required documentation mentioned in Section D.1 must be reviewed and approved by the Program and NIST.

3. Amendments to and Continuing Review of Animal Study Protocols

NIST requires documentation of annual continuing approval of all ASPs. Typically, ASPs are approved for no longer than a period of three years, with an annual IACUC review requirement. At the end of the three years, a completely new ASP is required for full review by the IACUC. The awardee is required to submit, as it occurs, documentation from the cognizant IACUC that continuing approval or a new approval of the ASP has been granted. If no changes are made to the protocol, documentation from the IACUC approving the annual renewal and indicating no changes to the study needs to be submitted to the Program. If

changes are made to the protocol, the revised protocol reviewed by the IACUC as well as the IACUC approval memo must be submitted.

In addition, NIST requires that all forms submitted to the IACUC required for initial or continuing approval be submitted to the Program. If your animal study requires approval by a safety, biohazard or other committee before the IACUC will approve the study, include documentation of the date those approvals were made and that they were submitted to the IACUC.

NIST requires that copies of any amendments to animal studies be submitted with the associated IACUC approval memo as they occur.

T. Contact Information

If you have any questions regarding the use of live vertebrate animals in research, please call the TIP Human and Animal Subjects Advisor at (301) 975-8779. The information contained in this booklet is also available on the TIP website at http://www.nist.gov/tip/helpful.htm .

U. Definitions

For the purposes of proposals and ongoing projects, the Program's definition of vertebrate animals used in research, as based on the regulation, is as follows:

Vertebrate Animal: Any live dog, cat, nonhuman primate, guinea pig, hamster, rabbit, or any other warm-blooded animal which is being used or is intended for use in research, teaching, testing, experimentation, or exhibition purposes.

In addition, the Program considers live vertebrate animals to include rats of the genus *Rattus*, mice of the genus *Mus*, birds, and any farm animal or other warm-blooded animal. Some uses of fish in research are also considered subject to these regulations.

The following additional definitions can be found in the Animal Welfare Act at 7 U.S.C. §§ 2131–2159 or in the National Research Council's *Guide for the Care and Use of Laboratory Animals* (the *Guide*).

Animal Study Protocol (Animal Care and Use Protocol): A document that is submitted to an IACUC that outlines the care and use of live vertebrate animals in a research setting. The *Guide* at pages 8-11.

IACUC: The Institutional Animal Care and Use Committee. The IACUC is appointed by the responsible administrative official at each institution and is charged with overseeing and evaluating the institution's animal program, procedures and facilities to ensure they are consistent with all applicable statutes, regulations and policies. The *Guide* at page 9.

APPENDIX 1: Applicable Authorities

Federal statutes, Executive Orders, federal regulations, policies, and guidelines have been issued concerning many types of research activities involving human subjects and live vertebrate animals. Although NIST may not be directly named in these authorities, to ensure that research involving human subjects funded by NIST is consistent with national policy, NIST hereby declares that it will fully adhere to these authorities. Shown below is a partial list of the statutes, regulations, policies, and guidelines applicable to research involving human subjects and research involving vertebrate animals. The proposer is advised to read and comply with all applicable authorities when submitting a proposal, or requesting to add research activities involving human subjects or live vertebrate animals to an ongoing Program award.

Human Subjects in Research

U.S. Department of Commerce. Protection of Human Subjects. 15 C.F.R. Part 27.
Available at: http://www.access.gpo.gov/nara/cfr/waisidx_02/15cfr27_02.html

U.S. Department of Health and Human Services Office for Human Research Protections__
Available at: http://www.hhs.gov/ohrp

U.S. Department of Health and Human Services. Protection of Human Subjects
(45 C.F.R. Part 46 Subparts B, C and D).
Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

Research involving the transplantation of human fetal tissue.
Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/fetal.htm

Vertebrate Animals in Research

Animal Welfare Act. 1966. Pub. L. No. 89-544, amended by 7 U.S.C. §§ 2131–2159.
Available at: http://www.aphis.usda.gov/ac/publications.html#awa

National Research Council. 1996. Guide for the care and use of laboratory animals.
Washington, D.C.: National Academy Press.
Available at: http://www.nap.edu/readingroom/books/labrats

The Office of Laboratory Animal Welfare of the Public Health Service
Available at: http://grants.nih.gov/grants/olaw/olaw.htm

APPENDIX 2: Human Subjects Determination Checklist

This checklist should be used to determine whether human subjects are involved in the research project and whether the research is exempt under the Department of Commerce regulations (see 15 C.F.R. Part 27) for the protection of human subjects. A proposal may contain more than one research activity involving human subjects, and each activity may require a different level of review. This checklist should be used for each potential use of human subjects. NIST and the Technology Innovation Program (TIP or "the Program") reserve the right to make an independent determination of whether your research involves human subjects. If NIST or the Program determines that your research project involves human subjects, you will be required to provide additional information for review and approval. A timeline for the submission of required documents can be found in Appendix 5.

A copy of this appendix may also be found at http://www.nist.gov/tip/helpful.htm**.**

1. Is there an intervention or an interaction with a living person that would not be occurring or would be occurring in some other fashion but for this research? Examples: videotaping people, observing children using software, surveying manufacturing personnel during a pilot test of new equipment, gathering tissue or cells from living human donors.

   ☐ Yes—Human subjects are involved. Go to question 3.

   ☐ No—Go to question 2.

2. a. Will data/information/specimens previously collected originally from people or about people be used in this research? Examples: broadcast video, web-use logs, medical information, cells or tissues, survey questions.

   ☐ Yes—Identifiable human subjects may be involved. Go to question 2.b.

   ☐ No—Go to question 6. It appears that human subjects may not be involved in the project. However, an exemption determination may be required if it is determined that human subjects are involved. Please review question 3 for additional information about research that may require either a determination of whether the activity is not considered a use of human subjects in research under the regulation or an exemption determination.

   b. Does that information contain private information in a form in which the identity of the subject is or may readily be ascertained from the information? Examples: medical records, donor name or address, sales transaction records.

   ☐ Yes—Identifiable human subjects are involved. Go to question 3 to see if an exemption may apply. If you know that an exemption does not apply, proceed to question 5.

   ☐ No—Go to question 3. The research may not be within the scope of 15 C.F.R. Part 27; however, it may require an exemption determination to be made due to the use of data, recordings, or specimens that could be linked to humans without appropriate safeguards.

3. Do you think the research task may either not be within the scope of 15 C.F.R. Part 27 or qualify for an exemption under 15 C.F.R. § 27.101(b)? The following questions will help you evaluate whether to request an exemption determination by NIST and the Program or provide documentation that the research may not be within the scope of 15 C.F.R. Part 27:

   a. Will the research task involving human subjects use only existing data, recordings (audio or visual), or specimens? Examples: patient records, a company's customer data, web-use logs, cells, or tissue.

      ☐ Yes—Go to question 3.d.

      ☐ No—Go to question 3.b.

   b. Will the research task involve only normal educational practices such as instructional strategies or comparison of instructional techniques, curricula, or classroom management methods? Examples: observation of student-teacher or student-computer interactions, video taping instructional approaches.

      ☐ Yes—Go to question 3.d.

      ☐ No—Go to question 3.c.

   c. Will the research task involve only educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior? Examples: broadcast video, software usage testing, recordings from security cameras.

      ☐ Yes—Go to question 3.e.

      ☐ No—Go to question 5. This research is probably not exempt and will require Institutional Review Board (IRB) review and approval.

   d. Do any of the data, recordings, specimens, or practices involve prisoners? Examples: testing educational software with prisoners, videotaping or surveying prisoners or detainees under the authority of a law enforcement entity.

      ☐ Yes—Go to question 5. This research is probably not exempt and will require IRB review and approval.

      ☐ No—Go to question 3.f.

   e. Do the procedures or observations of public behavior involve prisoners or children?

      ☐ Yes—Go to question 5. This research is probably not exempt and will require Institutional Review Board (IRB) review and approval.

      ☐ No—Go to question 3.h.

   f. Are the data, recordings (audio or visual), or specimens publicly available?
      NOTE: Publicly available may include items for sale, items that are freely available to the public, or items that reside in the public domain. Examples: customer data sets, catalog orders of cells or tissues, donations of pathological specimens, shareware.

      ☐ Yes—Go to question 4. This research may be exempt under 15 C.F.R. § 27.101(b).

      ☐ No—Go to question 3.g.

g. Will the data, recordings (audio or visual), or specimens be stripped of all identifiable information that could be linked to a human subject prior to being received by the investigator?

☐ Yes—Go to question 4. This research may not be within the scope of 15 C.F.R. Part 27, or this research may be exempt under 15 C.F.R. § 27.101(b).

☐ No—Go to question 3.h.

h. Will information be recorded by the investigator in such a way that it can be linked to the human subject? Examples: web-use logs tied to e-mail address, patient records, or specimens that include patient identifiers.

☐ Yes—Go to question 5. This research is probably not exempt and will need an IRB review.

☐ No—Go to question 4. This research may be exempt under 15 C.F.R. § 27.101(b).

4. An exemption under 15 C.F.R. § 27.101(b) may apply to the task, or the task may not be within the scope of 15 C.F.R. Part 27. In order to complete the necessary requirements for research considered exempt under 15 C.F.R § 27.101(b), review the TIP Program Guidelines and Documentation Requirements for Research Involving Human and Animal Subjects. A copy of that booklet can be obtained on the TIP website at http://www.nist.gov/tip/helpful.htm or by calling 1-888-TIP-NIST (1-888-847-6478) and requesting a copy. Complete Appendix 3 and/or Appendix 4 in the booklet as required and submit with your proposal or your request to add the research activity to an ongoing project. During the review of a proposal by the Evaluation Panel you may be asked for additional information. However, additional documentation to reach a final determination may also be requested after the proposal is funded.

5. An exemption probably does not apply to the proposed research, however further documentation may still be required. Review the TIP Program Guidelines and Documentation Requirements for Research Involving Human and Animal Subjects. A copy of that booklet can be obtained on the TIP website at http://www.nist.gov/tip/helpful.htm or by calling 1-888-TIP-NIST (1-888-847-6478) and requesting a copy. See Appendix 5 in the booklet for the required documentation list for your proposal or to add the research activity to an ongoing project. During the review of a proposal by the Evaluation Panel you may be asked for additional information. However, additional documentation to reach a final determination may also be requested after the proposal is funded.

6. It appears that human subjects are not involved in this project. This checklist is only a tool for general guidance and does not constitute a final legal opinion from NIST on whether or not human subjects are involved, or whether or not an exemption determination under the regulations is needed. If upon NIST and Program review of the proposed research it is determined that additional documentation is needed to reach a preliminary determination you will be asked to provide the additional documentation. During the review of a proposal by the Evaluation Panel you may be asked for additional information. However, additional documentation to reach a final determination may also be requested after the proposal is funded.

APPENDIX 3: Request for an Exemption from 15 C.F.R. Part 27 for Research Involving Human Subjects in Information Technology, Manufacturing, or Non-clinical Imaging Studies

Responses to the following questions must be supplied along with the initial proposal submission or when a request for exemption is made during an ongoing award, to allow NIST and the Technology Innovation Program (TIP or "the Program") to perform an independent determination of whether the use of human subjects qualifies for an exemption from the requirements of 15 C.F.R. Part 27. Keep in mind that the term data includes collection of data from voice, video, digital or non-clinical image recordings made for research purposes. To request exemptions for research activities contained in proposals or ongoing projects involving biological studies, complete the form attached as Appendix 4. If a question below is not applicable, please indicate "NA."

A copy of this appendix may also be found at http://www.nist.gov/tip/helpful.htm.

1. What is the time frame (start and end dates) for human subject/data/image involvement?
2. How is the project planning to use human subjects in the research?
3. State the technical justification for human subject/data/image involvement. Is there a way to achieve an equivalent technical outcome without this involvement? Explain.
4. Is any of the data preexisting?
    a. For the preexisting data, describe the data and how it is being obtained. Is it being obtained through a purchase, a donation from a source outside the project, or a project participant or collaborator?
    b. Are the data/images stripped of any identifiable information (e.g., personal identifiers such as names or codes that can be traced back to the human donor or source)? Explain.
    c. Are the data/images publicly available from a named source? Explain and name the source(s) being considered or planned, if appropriate.
    d. Please explain the terms under which you are obtaining the data.

    NOTE: An answer of "no" to question 4 may disqualify the research activity from exemption under 15 C.F.R. Part 27. In these cases, the proposal protocol/ task descriptions MUST be reviewed and approved by an IRB that possesses a current Federalwide Assurance appropriate for the research in question, on file with the OHRP. This IRB approval will be requested if the proposal is funded. However, during the review of a proposal by the Evaluation Panel you may be asked for additional information. Ongoing projects with IRB reviews should submit documentation as outlined in Chapter 1 Section F.
5. Are any data and images being collected for the express purpose of this research? Or is any of the data being collected during the project primarily for purposes other than this project?
    a. Please explain the source of the data/image/recording (e.g., video archives, proprietary database, security systems/records, medical records, video conference records).

b. What entity and/or individuals are collecting this data? What is their relationship to the project?

c. What is the extent of contact by these entities or individuals with the subjects?

d. What is the extent of control by these entities or individuals over the environment in which the human subjects will be monitored?

e. What is the extent of contact by anyone on the project or connected to an institution that is involved in the project.

6. Do the data/images/recording come from individuals (e.g., children or prisoners) who may need special safeguards?

   NOTE: An answer of "yes" to question 6 may disqualify the research activity from exemption under 15 C.F.R. Part 27. In these cases, the proposal protocol/ task descriptions MUST be reviewed and approved by an IRB that possesses a current Federalwide Assurance (FWA) appropriate for the research in question, on file with the OHRP. This IRB approval will be requested if the proposal is funded. However, during the review of a proposal by the Evaluation Panel you may be asked for additional information.

   Ongoing projects with IRB reviews should submit documentation as outlined in Chapter 1 Section F.

7. Is the image/recording an image/recording of only "public behavior"? Some indicators of public behavior are the following:

   a. The image of behavior does not give rise to any cause of action under any legal theory protecting personal privacy.

   b. There are no trade secrets or other confidential information pertaining to any person contained in the image or recording.

   c. There are no copyright restrictions, or the copyright holder has granted written permission to the proposer.

   d. The image of behavior contains any other matter the proposer deems germane to this issue.

8. If the answer to question 7 is "yes":

   a. Can the human subjects be identified directly or indirectly through identifiers?

   b. If the human subject can be identified, would any disclosure reasonably place the subject at risk of criminal or civil liability, or would it jeopardize standing, employability, or reputation?

9. Has the research been reviewed by an IRB? If yes, attach a copy of the review. (See Chapter 1, Section F)

The following signed statement must accompany the answers to the above questions:

This is an accurate description of the proposed research involving human subjects. Any changes in protocol or task descriptions will be submitted in advance to the IRB as appropriate and to the Program before notification of a decision for either a new award or an ongoing project .

_____ _____

Signature of Principal Investigator **Date**

APPENDIX 4: Request for an Exemption From 15 C.F.R. Part 27 for Research Involving Human Subjects in Biological Studies

Responses to the following questions must be supplied along with the initial proposal submission or when a request for an exemption is made during an ongoing project, to allow NIST and the Technology Innovation Program (TIP or "the Program") to perform an independent determination of whether the use of human subjects qualifies for an exemption from the requirements of 15 C.F.R. Part 27. To request exemptions for research activities contained in proposals or ongoing projects involving the collection of data from voice, video, or digital sources or involving other uses of informatics, complete the form attached as Appendix 3.

A copy of this appendix may also be found at http://www.nist.gov/tip/helpful.htm.

1. What is the time frame (start and end dates) for human tissue/subject involvement?
2. State the technical justification for human tissue/subject involvement. Is there a way to achieve an equivalent technical outcome without this involvement? Explain.
3. Are the samples stripped of any identifiable information (e.g., personal identifiers such as names or codes which can be traced back to the human donor or source)? Explain.
4. Is the tissue publicly available from a named source? Explain and name the source(s) being considered or planned, if appropriate.

   NOTE: An answer of "no" to either question 3 or question 4 may disqualify the project from an exemption. In those cases, an appropriate IRB approval may be required and should accompany the proposal if the work is within the first year of the project.
5. What is the anatomical source of the cell or tissue (e.g., liver, skin)?
6. What is the extent of tissue handling by the Principal Investigator: collecting, receiving, and/or sending specimens?
7. Are the samples preexisting, being collected for the express purpose of the research, or being obtained by some combination of the two?
8. Are the samples being "custom collected" from individuals who may need special safeguards (i.e., children, pregnant women, human fetuses, neonates, or prisoners)?

   NOTE: An answer of "yes" to question 8 may disqualify the research activity from exemption under 15 C.F.R. Part 27. In these cases, the proposal protocol/task descriptions MUST be reviewed and approved by an IRB that possesses a current Federalwide Assurance appropriate for the research in question, on file with the OHRP. This IRB approval will be requested if the proposal is funded, However, during the review of a proposal by the Evaluation Panel you may be asked for additional information.

   Ongoing projects with IRB reviews should submit documentation outlined in Chapter 1 Section F.
9. Has the research been reviewed by an IRB? If yes, attach a copy of the review. (See Chapter 1, Section F)

The following signed statement must accompany the answers to the above questions:

This is an accurate description of the proposed research involving human subjects/tissues. Any changes in protocol or task descriptions will be submitted in advance to the IRB as appropriate and to the Program before notification of a decision for either a new award or an ongoing project .

_____ _____

Signature of Principal Investigator **Date**

APPENDIX 5: Submission Timeline for Required Documentation—Human Subjects

Determination of Type and Date of Human Subjects Use As Indicated From Appendix 2	Initial Proposal or Current Project	Proposals Under Evaluation Panel Review or Current Projects
Occurring in any year of the project.	• Indicate on *Form SF-424 Research & Related Other Project Information*, whether your project involves exempt and/or non-exempt human subjects research activities and provide IRB and FWA information for the primary proposer or award recipient. • If more than the primary organization is involved in non-exempt human subjects research in the first year, the FWA numbers for engaged institutions should be included as part of the technical plan. • Clearly indicate why using human subjects is pertinent to a specific task in the proposed Technical Plan.	• Revise the *SF-424 (R&R) and the Research & Related Other Project Information* forms as appropriate if not completed correctly in the original submission. • Update any use of human subjects in research, as appropriate. • Update FWA or IRB information, as appropriate. • Any materials or clarifications requested by NIST to facilitate the NIST evaluation.
Non-use of biological materials or data from human subjects Year 1 of New Proposal or Current project year of an existing award.	• Completed answers to Appendix 3 and/or Appendix 4 as required. • Include signature of Principal Investigator on Appendix 3 and/or Appendix 4. • For proposals, include Appendix 3 and/or Appendix 4 as part of the consolidated file to be attached to the Research and Related Other Project Information form (see Chapter 5 of the TIP Proposal Preparation Kit).	• Complete answers to Appendix 3 or 4 if not previously submitted or incomplete (e.g. missing PI signature). • Any materials or clarifications requested by NIST to facilitate the NIST evaluation.

APPENDIX 5: Submission Timeline for Required Documentation—Human Subjects (cont'd)

Determination of Type and Date of Human Subjects Use As Indicated From Appendix 2	Initial Proposal or Current Project	Proposals Under Evaluation Panel Review or Current Projects
Exempt Research (Item 4 from Appendix 2) Year 1 of New Proposal or Current project year of an existing award.	• Indicate on the *SF-424 (R&R)* and the *Research & Related Other Project Information* forms, if your project involves exempt human subjects research activities and provide an estimate of the exemption type, if you have one. • Completed answers to Appendix 3 and/or Appendix 4 as required. • Include signature of Principal Investigator on Appendix 3 and/or Appendix 4. • For proposals, include Appendix 3 and/or Appendix 4 as part of the consolidated file to be attached to the Research and Related Other Project Information form (see Chapter 5 of the TIP Proposal Preparation Kit).	• Complete answers to Appendix 3 or 4 if not previously submitted or incomplete (e.g. missing PI signature). • Any materials or clarifications requested by NIST to facilitate the NIST evaluation.

APPENDIX 5: Submission Timeline for Required Documentation—Human Subjects (cont'd)

Determination of Type and Date of Human Subjects Use As Indicated From Appendix 2	Initial Proposal or Current Project	Proposals Under Evaluation Panel Review or Current Projects
Institutional Review Board (IRB) approval required (Item 5 from Appendix 2) Year 1 of New Proposal Or Current project year of an existing award.	• Indicate on the *SF-424 (R&R)* and the *Research & Related Other Project Information* forms, if your project involves non-exempt human subjects research activities and provide IRB and FWA information for the primary proposer or award recipient. **NOTE:** Initial proposals should include the following information within the proposed technical plan activities for Year 1, or on the NIST 1022B for applicable subcontractors. Current awards may submit in a separate document: • Name of all the organization(s) IRB(s) that will be reviewing the protocol(s) • If more than the primary proposer or award recipient is involved in non-exempt human subjects research in the first year, the Federalwide Assurance (FWA) number for each additional engaged institution should be included. • Provide the expected date of IRB review if it is pending.	• The expected date of submission of new protocol(s) to the IRB if the proposal is funded. • Or a signed and dated approval letter from the IRB indicating approval and expiration dates for each protocol, if they are ongoing protocols, and a copy of all documents approved by the IRB, including consent forms, screening scripts and advertisements • Any clarifications as requested by NIST to facilitate the NIST evaluation.
Deferred exemption or deferred IRB approval required After Year 1 in New Proposal Or Current project but in future project years and information not provided with original proposal	• No additional documents, beyond the *SF-424 (R&R)* and the *Research & Related Other Project Information* forms noted above, are required to be submitted with the initial proposal. • Current project participants should inform the Program's project manager when considering the addition of human subjects to a research task, which was not in the original proposal	• A projected date for human subjects research activities and a schedule of when NIST required documentation will be submitted: Note if the activity is expected to be exempt or if an IRB review may be required. • Include dates for obtaining FWAs and agreements with cognizant IRB(s), if these are not currently in place. • Any clarifications as requested by NIST to facilitate the NIST evaluation.

APPENDIX 6: Submission Timeline for Required Documentation—Live Vertebrate Animals

Date of Animal Use	Initial Proposal or Current Project	Proposals Under Evaluation Panel Review or Current Projects
Occurring in any year of the project	• Indicate on *the SF-424 (R&R) and the Research & Related Other Project Information* forms if the project requires animal studies and why using live vertebrate animals is pertinent to the specific task(s) in the proposed research plan. • If more than the primary organization will be involved in animal studies in the first year, the names of the additional applicable institutions should be indicated within the proposed technical plan, or on the NIST 1022B for subcontractors.. • Clearly indicate why using live vertebrate animals is pertinent to a specific task in the proposed technical plan.	• Revise the *SF-424 (R&R) and the Research & Related Other Project Information* forms as appropriate if not completed correctly in the original submission. • Update any use of live vertebrate animals in research, as appropriate. • Any clarifications as requested by NIST to facilitate the NIST evaluation.
Institutional Animal Care and Use Committee (IACUC) approval required Year 1 of New Proposal or Current project year of an existing award.	**NOTE:** Initial proposals should include the following information within the proposed technical plan activities for Year 1, or on the NIST 1022B for applicable subcontractors. Current awards may submit in a separate document: • Location and name of all organizations where live vertebrate animals will be used for Year 1 research tasks and/or housed for general care. • Name of each IACUC that will be reviewing and approving each Animal Study Protocol (ASP) and type of assurance. • Timeline for the use of live vertebrate animals in Year 1; the estimated date of IACUC approval; and when the ASP will be submitted to NIST for review if the proposal is funded.	• Signed and dated copy of each of the IACUC-approved ASPs will be required if proposal is funded. • Documentation of each IACUC approval indicating the approval and expiration of the ASP will be required if proposal is funded. • Any clarifications as requested by NIST to facilitate the NIST evaluation.

APPENDIX 6: Submission Timeline for Required Documentation—Live Vertebrate Animals (cont'd)

Date of Animal Use	Initial Proposal or Current Project	Proposals Under Evaluation Panel Review or Current Projects
Deferred Institutional Animal Care and Use Committee (IACUC) approval required After Year 1 in New Proposal Or Current project, but in future project years and information not provided with original proposal	• No additional documents, beyond the *SF-424 (R&R) and the Research & Related Other Project Information* forms noted above, are required to be submitted with the initial proposal. • Current project participants should inform the Program's project manager when considering the addition of live vertebrate animals to a research task which was not in the original proposal.	• Timeline for the use of live vertebrate animals; the estimated date of IACUC approval; and when the ASP will be submitted to NIST for review if the proposal is funded. • Name of each IACUC that may be reviewing and approving each ASP. • Any clarifications as requested by NIST to facilitate the NIST evaluation.

APPENDIX 7: Common Documentation Issues

Certain issues with documentation can delay the evaluation of requests for use of human subjects and live vertebrate animals in research. The following is a list of several common issues we see, as well as suggestions on how to avoid them in the preparation of your request.

A. Submission of an incomplete protocol, or a protocol that lacks sufficient detail for reviewers to fully understand the study design and plan and how it fits within the project. It is important that the protocol adequately describe the study and what the investigator hopes to learn from the study. For ongoing projects and proposals under review by the Evaluation Panel the Program can provide comments on drafts of the protocol before final IRB or IACUC review to help identify questions or concerns that may occur during later NIST review. Comments on draft protocols do not constitute final approval or a guarantee that no other additional issues may come to light in the final review. It is also advisable to obtain in advance the protocol expectations from the IRB or IACUC that will be reviewing the protocol. ***The following information <u>should not be lacking</u> as part of a well written protocol:***

1) A clear definition of study objectives is needed, which may or may not require background information on the study or device is required.

2) The rationale for the use of live vertebrate animals (animal protocol) or the use of the desired subject population (human studies protocol) is required. This section should also note anticipated recruitment procedures for human studies.

3) A detailed description of the experimental design including the procedures to be employed should be included. If an experimental device is being used, include a description of that device and how it will be used.

4) The risks of the research project must be explained.

   a) For animal studies, this includes pain and distress classification as well as how these are to be monitored and alleviated. Animal protocols are also expected to include a description of animal care procedures before, during, and after experimentation as well as anesthesia and analgesia agents and anticipated disposition of animals at the conclusion of the study.

   b) For human studies, descriptions of all of the anticipated risks that human subjects may experience are needed. Also, potential benefits to the subject, adverse event reporting procedures, costs, and data confidentiality should be explained in human studies. This information is also expected to be included in common language in the consent form.

5) A summary description of all the data to be collected and how it will be analyzed.

6) Final protocols should be signed by the principal investigator and clearly note the date that it was reviewed and approved by the IRB (human studies) or the IACUC (animal studies).

7) All of the elements in a study are expected to be coordinated and not appear to be in conflict with each other.

   a) For human studies, if changes are made in the protocol, the consent form should clearly reflect the changes applicable to obtaining informed consent. The description of the research activities in the protocol are expected to be consistent with the description of research activities in the advertisement to solicit volunteers. Paying close attention to the details in protocols, consent forms, HIPAA waivers, and recruiting materials ensures that there is consistency in the package being submitted for review. All recruiting and subject screening materials need to be consistent with any inclusion and exclusion criteria defined in the protocol.

   b) For animal studies, if a change is made in the type and/or overall number of animals to be used, the revised or amended protocol should reflect those changes.

8) For human studies, consent forms should not be lacking important details. For example, the following issues must be addressed in consent forms:

   a) Identity of the person to be notified in the event of an injury. The name, study position, and phone number should be provided for this person, if applicable, in the relevant section of the consent. The word "injury" must be used in this statement.

   b) All people who may have access to study results are expected to be listed. As noted in the Consent section above, a statement that OHRP, NIST, and other federal officials as appropriate have the ability to audit study records if deemed necessary should be included.

   c) Discussion of payment methods for volunteers and how payment is handled in the event of withdrawal of a volunteer from the study or only partial completion of the study should be included. How and when a volunteer is compensated is also needed if that is part of a study design. This may not be included in the benefits section of the consent form.

   d) Discussion of the procedures for how withdrawal of a volunteer impacts data collected up to receipt of the withdrawal notification.

B. Some general administrative details can also delay processing requests. Please be sure that the following issues are appropriately addressed in your submission or when requested while your proposal is under review by the Evaluation Panel or by the Program for ongoing projects:

1) NIST must receive a copy of any document that was submitted to an IRB or an IACUC for review. This also includes any relevant correspondence or responses to IRBs or IACUCs. Failure to do this can result in delay of the review of the package by NIST.

2) Submitted documents must be signed. Signatures are often missing when documents are emailed. NIST requires that all documents in the final submission package be signed where indicated if signed documents were submitted to the IRB or the IACUC. If the IRB has a published policy of accepting unsigned documents via email, documentation of that IRB policy will be requested.

3) If any participating company changes names, updated documentation to the cognizant review committee (IRB or IACUC) and updated assurance certifications will be required:

   a) For human subjects research: updated FWA and linkage to the cognizant IRB is required.

   b) For live vertebrate animals in research: updated OLAW certification, USDA registration, or AAALAC accreditation is required.

   c) Updated documentation to the cognizant review committee should show the company name change.

   d) Updated approval by the IRB or IACUC reflecting the name change.

4) Animal study protocols that include significant surgical interventions must be signed by a veterinarian as well as by the principal investigator.

5) All final consent forms for human studies should have an IRB stamp and date showing that it was reviewed and approved by the IRB.

6) All organizations that are "engaged" in non-exempt human subjects research are required to have a Federalwide Assurance that is linked to the IRB doing the review, even if each organization is involved with only a part of the study. One central IRB that is linked to each organization's FWA may do the review. However, some institutions require their IRB to review all protocols and do not prefer the use of a central IRB. In this case, each organization will link their FWA to their cognizant IRB. The award recipient, or ongoing project lead needs to make sure that each IRB reviews the same protocol when multiple IRBs are used. Using multiple IRBs can take more time for the IRBs to process and for NIST to process, since each IRB may request changes that then have to be approved by all the other IRBs. If a multiple IRB review is required, each IRB must

receive the complete protocol package for review so that each IRB understands the entire study in detail. If multiple IRBs are involved, then all IRBs must approve any changes made to the study documentation, and NIST must conduct a separate review and evaluation of each IRB's approval. All documentation sent to each IRB for approval must also be sent to NIST.

7) Be consistent in identifying the individual affiliations of study personnel, especially when personnel have multiple affiliations (i.e., a professor is also a part-time employee of a participating company). Individual affiliations must be consistent with how the individual's time is being funded during the study.

8) If study personnel have an economic interest in the study results, that interest must be identified with a letter from that individual stating that fact and where the conflict of interest information for the study is maintained. This information is usually required by the IRB; therefore, the Program requires a copy of this as well.

9) Research personnel on submitted studies may not be a voting member of the approving oversight committee (i.e. IRB or IACUC). This may be or may give the appearance of a conflict of interest.