CPHS

Policies and Procedures



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About CPHS

Institutional Authority

The California Health and Human Services Agency (CalHHS) established the Committee for the Protection of Human Subjects (CPHS), an Institutional Review Board (IRB), in July 1976 to review research projects involving human subjects under the federal Common Rule. CPHS is bound by the terms of the Federalwide Assurance (FWA) 00000681 signed with the U.S. Department of Health and Human Services (HHS), Office for Human Research Protections (OHRP). CPHS is the only IRB empowered by CalHHS.

In 2006, changes to Civil Code section 1798.24(t) established requirements for CPHS to use in reviewing the release of identifiable state data by any state department for research.

CPHS adopts these policies and procedures to implement its duties under the federal regulations for the protection of human subjects (45 CFR Part 46, 21 CFR Part 50 and 21 CFR Part 56) and Civil Code section 1798.24(t).

Purpose of the CPHS

CPHS has three functions:

1) To review all releases of confidential state data for research projects by **any state department** which includes but is not limited to:

    a. Reviews to determine whether requests for California state death data have valid scientific interest; and/or

    b. Review of Sudden Infant Death data requests.

    c. Note: according to the Civil Code section 1798.24(t), confidential means: any personal information in a manner that would link the information disclosed to the individual to whom it pertains. Personal information means: any information that is maintained by an agency that identifies or describes an individual, including, but not limited to, the individual's name, social security number, physical description, home address, home telephone number, education, financial matters, and medical or employment history. It includes statements made by, or attributed to, the individual.

2) To review research involving human subjects in which CalHHS is engaged, as defined below.

3) To review research studies described in 1) or 2) as a Privacy Board under 45 CFR 164.500

CPHS is required by law to review research requests for state data under the criteria listed in Civil Code section 1798.24(t). CPHS conducts reviews of research involving human subjects in compliance with the federal regulations (including both the Common Rule and the Food and Drug Administration), and state law.

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When a research project involves requests for both state data and CalHHS is engaged in research involving human subjects, CPHS is governed by both the Civil Code criteria and the Federal Regulations for the conduct of research (45 CFR 46, 21 CFR Part 50 and 21 CFR Part 56). For these projects, the Committee will review the request for state data using only the criteria in the Civil Code. For research that is not regulated by the FDA, the Committee utilizes the Common Rule criteria to approve research (45 CFR 46.111) and considers the ethical principles of the Belmont report when reviewing the portion of the research that involves human subjects. Definitions of CalHHS engagement are included under Authority of CPHS of this policy.

Additionally, when applicable, CPHS reviews research involving investigational drugs or devices under Title 21, Parts 50, 56, 312 (drugs and biologics), and 812 (devices) of the Code of Federal Regulations (FDA Regulations). For more information, see the polices on Drugs and Devices.

When reviewing a study which includes Protected Health Information (PHI), CPHS will review the study under the Health Insurance Portability and Accountability Act (HIPAA). For more information, see Privacy Policy.

Principles Governing the CPHS

For all research involving human subjects for which CalHHS is engaged, CPHS is governed by the ethical principles delineated in The Belmont Report, issued by the Department of Health, Education, and Welfare in April 1979. These include:

Respect for Persons
Respect for persons incorporates at least two ethical convictions: first, those individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

Beneficence
Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

Justice
The selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reason directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Authority of CPHS

CalHHS or its departments are considered engaged in research if any of the following are true:

1) CalHHS or its departments receive federal funding to conduct research, regardless of whether CalHHS staff carry out the research or subcontract it out;
    a. For non-federally funded projects, CalHHS or its departments execute a contract to conduct research. CalHHS grants do not constitute a contract;
2) CalHHS or departmental staff:
    a. intervene for research purposes with any human subjects of the research by performing invasive or noninvasive procedures;
    b. intervene for research purposes with any human subject of the research by manipulating the environment;
    c. interact for research purposes with any human subject of the research, such as, conducting surveys, interviews, and focus groups;
    d. obtain informed consent of human subjects for the research. Merely distributing research materials, such as recruitment documents, does not constitute obtaining informed consent; and/or
    e. obtain for research purposes identifiable private information or identifiable biological specimens from any source for the research. For example, secondary use of administrative personally identifiable data for research purposes, even if originally collected by CalHHS or its departments for administrative purposes.
3) CalHHS or departmental staff release to external researchers personally identifiable information to be used to contact participants as part of recruitment, screening, or informed consent activities.

When CalHHS is engaged solely under this criterion, CPHS review authority is limited to the activities creating that engagement. Accordingly, CPHS review is limited to:

- recruitment methods and materials;
- screening procedures and instruments;
- the informed consent process;
- and those portions of the informed consent document directly related to participant recruitment and enrollment.

CPHS will not (and does not have purview to) review or approve the remaining aspects of the research protocol, including the scientific design, study procedures occurring after enrollment, data collection, statistical analysis, or continuing oversight of the study, unless CalHHS is engaged under one or more additional engagement criteria described in this policy.

Note: Releasing personally identifiable data to external researchers for secondary data analysis does not constitute CalHHS staff or agent engagement in research under the Common Rule. Additionally, all releases of personally identifiable data for research purposes must be approved by CPHS under the California Information Practices Act (Civ. Code § 1798.24(t)).

CPHS has jurisdiction over:

1) All research involving subjects for whom the CalHHS or its components have direct responsibility, such as patients in state hospitals

2) Projects for entities for which a local IRB exists (e.g., public entities such as a public

university), as well as entities that do not have their own IRB, such as a county.

3) Projects when the CPHS has a contract with another IRB authorizing the review consistent with the federal Common Rule (see Reciprocity with other Institutions below).

Departments within CalHHS required to submit research to CPHS include:

- California Department of Aging
- California Department of Child Support Services
- California Department of Community Services and Development
- California Department of Developmental Services
- California Department of Health Care Services
- California Department of Managed Health Care Services
- California Department of Public Health
- California Department of Rehabilitation
- California Department of Social Services
- California Department of State Hospitals
- Emergency Medical Services Authority
- Department of Health Care Access and Information
- Office of Youth and Community Restoration

If the project meets the definition of human subjects research but does not include access to or use of state data, CPHS review is limited to the requirements listed in 45 CFR 46.111 and/or 21 CFR 56.111.

Definitions for CPHS Use

CPHS applies all definitions in 45 CFR 46.102, 21 CFR 50.3, and 21 CFR 56.102, as appropriate, including: research, human subjects, clinical trial, clinical investigations, etc, in the committee's review and assessment of projects submitted for review. A list of acronyms and definitions can be found in Appendix A and B, respectively.

Communications with other State Agencies/Offices

CPHS will establish working relations with other state agencies, offices, and departments within CalHHS to coordinate research protection related activities. CPHS may also coordinate with other institutions, or external IRBs, for multi-site research.

Reciprocity with Other Institutions

Reliance Agreements, Single IRB Review, and IPA Review

CPHS may enter into reliance agreements with other appropriately constituted IRBs when permitted by federal regulations, state law, and institutional policy.

For federally funded cooperative research subject to the Common Rule single IRB (sIRB) requirement (45 CFR 46.114), CPHS will comply with applicable federal mandates and may either:

1. Serve as the Reviewing IRB for participating institutions; or
2. Rely upon the external Reviewing IRB designated for the research.

When CPHS relies upon an external IRB, CPHS retains responsibility for ensuring compliance with California state law, including the Information Practices Act (IPA), institutional requirements, and any other requirements that are not delegated through the reliance agreement.

If CalHHS is engaged solely through the release of identifiable information for participant recruitment, screening, or informed consent activities, CPHS review remains limited to those activities. Nothing in this Reliance policy shall be interpreted as expanding CPHS review authority beyond the activities that establish CalHHS engagement.

CPHS review of requests for state-held personally identifiable information under Civil Code section 1798.24(t) may not be delegated through a federal single IRB arrangement unless expressly authorized by state law and a written agreement approved by CalHHS.

Projects undergoing review solely under the Information Practices Act are not considered to be under IRB review authority unless CalHHS is engaged in human subjects research. In such instances, CPHS acts in its capacity as the entity authorized to review disclosures of state-held information and not as an Institutional Review Board. Accordingly, federal single IRB requirements do not apply to IPA-only reviews.

Procedures for Reliance and Single IRB Review

1) During administrative review, CPHS staff will determine whether the project is:
    a. Subject to federal single IRB requirements;
    b. Subject to FDA regulations;
    c. Subject only to the California Information Practices Act; or
    d. Subject to both federal regulations and the Information Practices Act.
2) If a federal single IRB mandate applies, CPHS will determine whether:
    a. CPHS will serve as the reviewing IRB; or

b. CPHs will rely upon an external reviewing IRB.

3) If CPHS serves as the reviewing IRB for external institutions:

   a. A reliance agreement must be executed before research activities begin;

   b. The CPHS PI will ensure that each site relying on CPHS will receive site approval before beginning activities;

   c. Sites relying on CPHS retain local authority as defined within the reliance agreement but will comply with CPHS policies and procedures.

4) If CPHS relies upon an external reviewing IRB:

   a. A reliance agreement must be executed before research activities begin;

   b. Investigators remain responsible for compliance with CPHS reporting requirements regarding state data and IPA obligations; and

   c. CPHS retains authority to review and approve any release of state-held personally identifiable information.

5) For IPA-only reviews, CPHS will review the request under Civil Code section 1798.24(t) and will not apply IRB approval criteria unless CalHHS is engaged in human subjects research.

California Health and Human Services Agency (CalHHS) Responsibilities

Reporting Responsibilities

CPHS will report the following IRB determinations and issues to the Secretary of the California Health and Human Services Agency, the U.S. Office of Human Research Protection (OHRP), the Food and Drug Administration (FDA), the funding agency (whether federal, state, or private), the Principal Investigator (PI) and the Responsible Official (RO) of the project:

- Unanticipated problems and unanticipated adverse device effects;
- Serious and/or continuing noncompliance;
- Research misconduct (e.g., plagiarism, misrepresentation of study findings (falsification) and fabrication of data); and
- Suspensions or terminations of research under the authority of the CPHS.

The Secretary of CalHHS is the signatory of CalHHS' FWA and shall serve as the authorized Institutional Official (IO). The Secretary is responsible for appointing the CPHS Chairperson and CPHS members.

As the IO, the Secretary is responsible for that CPHS functions effectively and that the institution provides the resources and support necessary to comply with all requirements applicable to research involving human subjects.

Additional responsibilities of CalHHS (and the IO) include but are not limited to:

- Providing written assurance of compliance with requirements of 45 CFR Part 46 in the FWA to HHS.
- Enforcing policies requiring that all research CalHHS or its departments are engaged in and/or disclosing personally identifiable information held by CalHHS departments is reviewed and approved by CPHS, unless otherwise exempted by CPHS or when CPHS has deferred review via a reliance agreement to another appropriately constituted IRB.
- Providing sufficient professional staff or consultants to support the activities of CPHS.
- Setting expectations among CalHHS appointing authorities that CPHS members who are CalHHS employees will be making a significant time commitment to the CPHS, up to 10% effort.
- Supporting measures to educate CPHS members about protections for human subjects.
- Maintaining open channels of communication between CPHS members, staff, subjects, Researchers, and other interested parties both within and outside of CalHHS.
- Assuring that CalHHS executive and legal staff are available to provide guidance to CPHS, department heads, and other officials with responsibility for oversight of research.
- Appropriately sanctioning investigators who do not conduct research in accordance with CPHS requirements and determinations, who violate Federal regulations, or who knowingly compromise the rights and welfare of human subjects.

In compliance with the federal regulations and the IPA, CalHHS officials may not approve research involving human subjects or release of state data if CPHS has not approved it. However, CalHHS may disapprove the conduct of research even when CPHS has approved it.

Reporting Complaints

Concerns, complaints, or allegations regarding the conduct of human subjects research, the actions, policies or procedures of CPHS must be appropriately handled and investigated in a consistent and timely manner.

Any person who has a concern or complaint should contact:

California Health and Human Services Agency
Committee for the Protection of Human Subjects
2870 Gateway Oaks Drive, Suite 200, Sacramento CA 95833
Phone: (916) 651-5599
Email: cphs@otsi.ca.gov

The CPHS Administrator is responsible for ensuring that all concerns, complaints, and allegations have been appropriately addressed and will escalate as appropriate.

Alternatively, concerns and complaints can be forwarded to the Secretary, CalHHS at CHHSMAIL@chhs.ca.gov or support@chhs.ca.gov. Individuals are encouraged to include the following in the subject line of the correspondence: "**CPHS Concerns**." You may also call (916) 654-3454.

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Determinations of Research

In accordance with federal regulations and state law, the CPHS must approve any non-exempt human research conducted by or funded by (regardless of original source) the CalHHS and its 13 component departments prior to the initiation of the research (see section on Jurisdiction above). This policy provides information related to determining whether an activity is research involving human subjects and covered by the Federal Regulations.

In general, any non-exempt activity that meets either (a) the HHS definition of both "research" and "human subjects" or (b) the FDA definitions of both "clinical investigation" and "human subjects" is considered human research and requires review and approval by the CPHS.

Procedure for Determinations of Research

1) It is the responsibility of each investigator conducting non-exempt research conducted by or funded by the CalHHS to seek CPHS approval prior to initiation of the research project.

2) Investigators should reference this policy and federal regulations to make a preliminary decision regarding whether the project meets the OHRP definitions of research and human subjects or the FDA definitions of clinical investigations and human subjects.

    a) The investigator may contact the CPHS Office for guidance on the application of federal regulations and this policy.

    b) Failure to obtain CPHS approval prior to initiating non-exempt research may be considered serious non-compliance and may jeopardize the investigator's ability to receive IRB approval to conduct research involving human subjects under CPHS authority in the future.

3) In order to obtain an official determination from the CPHS as to whether the project constitutes research involving human subjects, investigators should submit an application within the CPHS electronic IRB system.

4) CPHS staff will review submitted applications for determinations to confirm all appropriate information has been submitted.

5) Once complete, CPHS staff will assign determination applications to the CPHS Administrator, Chair, or Vice-Chair to assess:

    a) If the project meets the definition of research and human subjects according to OHRP; or

    b) If the project meets the definition of a clinical investigation and human subjects according to the FDA.

6) If a project is determined to constitute research involving human subjects according to either 5(a) or 5(b), CPHS will determine the scope of its review authority. This will consist of:

        a) Complete IRB review for either an exemption determination or expedited/full board review;

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b) Limited-scope review of recruitment, screening, and informed consent activities; or

c) Information Practices Act review only

d) Or a combination of a & c or b & c.

If CPHS conducts a limited-scope review, the determination letter shall identify the activities reviewed by CPHS and state that all remaining portions of the research remain under the authority of another IRB.

7) Investigators will be informed of the CPHS determination of whether the project constitutes research.

   a) Investigators conducting projects which do not constitute research will receive a final letter and the electronic submission will be closed. Any future changes to the project would require a new submission to CPHS for consideration.

   b) Investigators conducting projects which constitute research will be instructed to submit an exempt or initial submission packet for CPHS.

Determining When Research Involving Human Participants Begins and Ends

1) Research begins when a researcher first "obtains data through intervention or interaction," or otherwise obtains "private information."

2) Screening activities and pilot testing are part of the research process and must be reviewed and approved (or an exemption issued) before those activities can begin.

3) Research ends when the study has been closed by the PI or terminated by the IRB. Research remains subject to CPHS oversight until such time as the project has been closed by the PI.

4) Researchers are encouraged to de-identify research data (i.e., remove all personal identifiers including name, email address, phone number, etc.) at the earliest opportunity. Once all personal identifiers and links to identifiers are destroyed, the research is no longer regulated under federal regulations; however, data use must still comply with the terms of any agreement (e.g., data use agreement) between the PI and CalHHS.

5) Secondary analysis of data collected as part of a previous study that retains identifiers must be submitted to the CPHS for approval or exemption. The submission must include information regarding the primary data collection, including the original informed consent document(s). The language of the original consent is a factor in the IRB's determination of whether secondary data analysis may be conducted and should therefore be included in the initial submission to the IRB.

California State Statutes Pertaining to Human Research

CA Family Code

Minor Consent (Sections 6920-6929): Describes when minors (children) may consent for themselves.

Emancipated Minors (Sections 7000-7002; 7050-7052; 7120-7123): Defines an emancipated minor and rights of emancipated minors.

CA Health and Safety Code

Protection of Human Subjects in Medical Experimentation Act (Sections 24170– 24179.5): Describes the informed consent process and requires that the "experimental subject's bill of rights" be provided to all research subjects in medical experiments.

Experimental Use of Drugs and Consent for Minors Provision (Sections 111515– 111545): Minor consent is required prior to administering an experimental drug. Parental or legal guardian consent (permission) is required and minor consent (assent) is required for children 7 years of age or older.

Surrogate Decision Maker (Section 24178): With respect to medical experiments that relate to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of adult research participants, investigators may obtain surrogate informed consent following a specific hierarchy for nonemergency and emergency room environments.

Mandatory Reporting of Sexually Transmitted Disease (Section 120500 -120605): Describes the requirements for reporting sexually transmitted disease to CA Department of Health.

CA Education Code

Parental Consent for Children to Participate in Research (Section 51513): For K-12 students - tests, questionnaires, surveys, or examinations containing any questions about the pupil's or the pupil's family's personal beliefs or practices in sex, family life, morality, and religion require written parental consent (permission).

CA Penal Code

Mandatory Reporting of Child Abuse or Neglect (Section 11164 -11174.3) Identifies who is a "mandated reporter" required to report known or reasonably suspected child abuse or neglect.

Prisoners in Biomedical and Behavioral Research (Section 3500 – 3523) Describes the requirements for biomedical and behavioral research conducted in CA prisons.

CA Welfare and Institutions Code

Elder Abuse and Dependent Adult Civil Protection Act (Section 15600 - 15637) Describes the requirements for reporting harm and neglect to elder or dependent adults.

CA Civil Code

HIPAA Research Authorization (Section 56.11(b)) Describes the requirement for a separate HIPAA authorization form.

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IRB Composition and Function

CPHS Members are appointed by and serve at the pleasure of the Secretary of CalHHS. Membership must fulfill the requirements of 45 C.F.R. Part 46.107 and 21 CFR 56.107 and includes the following:

1) CPHS must have at least five (5) members, with varying backgrounds and fields of expertise.

2) CPHS may not exceed thirteen (13) appointed primary members. There is no limit on the number of alternate members that may be appointed.

3) Members must be knowledgeable in the areas of research that CPHS reviews.

4) For review of research involving a vulnerable category of subjects, at least one member must be knowledgeable and experienced in working with that vulnerable population (e.g., a prisoner advocate).

5) CPHS shall have at least one (1) member whose primary expertise is in scientific areas and at least one (1) member whose primary expertise is in nonscientific areas.

6) CPHS must have at least one (1) member not affiliated with CalHHS directly or through an immediate family member.

7) Alternate members may be appointed by the Chair and Vice Chair to attend meetings at the invitation of the Chair to replace members not in attendance or if their expertise (i.e., prisoners) is needed to review a research request.

8) Every effort will be made to ensure that the CPHS has a diverse membership, including the use of inclusive outreach and recruitment efforts conscious of race, gender, age and cultural background.

For the purposes of this policy document, use of the term “Chair” refers to both the Chair and Vice-Chair of CPHS, except in the specific sections for those titled positions below.

Appointment of CPHS Members

Nominations for membership may be submitted to the CPHS Administrator by CalHHS department heads, any CalHHS employee, or members of the public. Such nominations must include the curriculum vitae and a list of references for the person being nominated.

The CPHS Administrator will pre-review all nominations, create a file for the candidate, and forwards nominations to the Chair for review.

When the Chair determines that appointment of a new member is necessary to maintain compliance with the regulations, to handle increased workload, or upon request of the CalHHS Secretary, the Chair will forward a prioritized list of candidates, with the curriculum vitae and reference list, to the CalHHS Secretary.

The following factors may be considered by the Chair when prioritizing candidates:

1) Knowledge of general principles of scientific research.

2) Expertise in research with vulnerable populations (e.g., pregnant women, children, prisoners, those who are socially or economically impaired, mentally impaired persons).

3) Expertise in research subjects of special importance to CPHS (e.g., pharmacology, genetics, and social science).

4) Ability to represent the needs of vulnerable ethnic and diverse population groups (e.g., ethnic minorities, children, and prisoners).

5) Knowledge of the principles of ethical research.

6) Ability to represent the research needs of specific CalHHS departments.

7) Knowledge of data privacy and security

CPHS members are appointed to three (3) year terms which are renewable based upon recommendations from the CPHS Administrator and Chair and at the discretion of the CalHHS Secretary. Renewal of terms is contingent upon fulfillment of the duties and responsibilities designated below. If reappointed, additional terms will also be for three (3) years. There is no limit to the number of terms that members may serve.

The CPHS Administrator and Chair can, at any point, recommend to the Secretary that a member be terminated for failure to carry out their duties in a timely, professional, or competent manner. The Administrator, with input from the Chair, must document the reason for termination in a letter to the Secretary, who will make the final determination.

Duties and Responsibilities

CPHS members are provided with continuing education on an ongoing basis as part of each meeting's standard agenda. The education topic is generally selected to coincide with an issue from one of the studies scheduled for review at the current or previous meeting(s).

CPHS Primary/Regular Members are expected to:

1) Attend at least 80% of full board meetings annually based on a calendar year.

    a) Board members must attend at least 65% of board meetings in-person in order for CPHS to comply with Bagley-Keene meeting requirements. This requirement ensures that CPHS is able to regularly meet to conduct business.

        i. The Chair retains the authority to allow members to attend virtually meeting provided that prospective notice is provided of remote attendance and quorum requirements will not be impacted; however, regular in-person attendance is expected for board members.

    b) Board members are expected to be in attendance for the entirety of the board meeting.

    c) Board members may attend no more than one (1) full board meeting remotely per

calendar year without prior approval from the CPHS Administrator and/or Chair.

d) Absences at more than one-third of meetings within a 12-month period may constitute grounds for dismissal.

e) Members who cannot attend a meeting or need to leave a meeting early are expected to notify the Administrator in advance of the meeting and are expected to review and provide feedback about continuing review projects for which they are the designated primary reviewer.

2) Be familiar with all projects to be reviewed at each meeting and inform the Administrator if they have any substantive concerns.

3) Comply with all CPHS policies and procedures, as well as federal, state and local regulations, policies or guidelines relating to research involving human participants.

4) Treat all researchers, regardless of experience or background, with respect and courtesy.

5) Members who are assigned new research for review by expedited procedures will ensure the review is completed in a timely manner.

6) Complete appropriate education in research ethics, human research protections, IRB responsibilities and regulatory policy within six (6) months of appointment to the board.

7) Attend an orientation with the CPHS Office that includes review of the CPHS electronic system, CPHS Policies and Procedures, forms and checklists, and other pertinent information following appointment as a CPHS member and prior to serving as reviewers (primary or secondary). This training requirement includes ex-officio members and alternate members.

8) Disclose any actual, potential, or perceived conflicts of interest (COI) with research under review by CPHS.

9) Update the CV on file with the CPHS Office every three (3) years.

CPHS Chairperson

Selection and Appointment

The Chair is nominated by the CPHS Administrator and then submitted for appointment by the Secretary of CalHHS. The Chair must have been a member of the CPHS for at least two (2) years. The Chair serves at the discretion of the Secretary of CalHHS. After three (3) years of service, the Chair is eligible for additional three year term of service as Chair upon reappointment by the CalHHS' Secretary.

Duties and Responsibilities

In addition to the responsibilities of all CPHS members, the CPHS Chairperson will:

1) Assures that the CPHS operates in accordance with the terms of the FWA (shared responsibility with the Administrator) and informs the CalHHS Secretary regarding problems that inhibit the CPHS from fulfilling its functions.

2) Ensures that CPHS operates within its authority and consistent with Civil Code section 1798.24(t) as well as federal, state and local regulations, policies or guidelines related to research involving human subjects.

3) Advises the Secretary of CalHHS regarding appointment of new CPHS members.

4) Advises Researchers both within and outside CalHHS regarding the purpose and functioning of the CPHS.

5) Determines projects that need verification of information from source(s) other than the Researcher, including whether material changes have occurred in a project since the last CPHS review.

6) Advises the CPHS Administrator regarding daily functioning of the CPHS.

7) Assists the CPHS Administrator in responding to inquiries from Researchers and others both within and outside of CalHHS.

8) Proposes policy and procedure changes for CPHS.

9) Represents CPHS at CalHHS meetings, as well as at national meetings.

10) Chairs all convened CPHS meetings. If unable to attend, the Chair arranges for meetings to be chaired by the Vice Chair.

11) Ensures federal review criteria (45 CFR 46.111 and 21 CFR 56.111) are met, and determinations made by CPHS members are appropriate.

12) Reviews project applications through the expedited review process.

13) Collaborator with CPHS members in reviewing applications as a primary or secondary reviewer.

14) Reviews submissions and other documents in advance of the CPHS meeting and is prepared for discussion on agenda items.

15) Provides education to members regarding recent changes in federal policies or regulations, state law, and best practice (joint responsibility with CPHS Administrator).

16) Reviews requests for not research, not human subjects research (NHSR), and exemption determinations in collaboration with the CPHS Administrator.

17) Suspends research when appropriate.

18) Collaborates with the CPHS Administrator to resolve CPHS-related issues with researchers or participants.

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CPHS Vice-Chairperson

Selection and Appointment

The Vice-Chairperson is selected and appointed by the CPHS Chair with approval of the Secretary of CalHHS. The Vice-Chair must have been a member of the CPHS for at least one (1) year. The Vice-Chair serves at the discretion of the Chair and can be relieved of their duties at any time.

Duties and Responsibilities

In addition to the responsibilities of all CPHS members, the CPHS Vice-Chair:

1) Assumes responsibilities of the Chair when the Chair is unavailable.

2) Participates in subcommittees when requested by the Chair.

3) Supports the Chair in ensuring that the CPHS complies with its FWA and the Civil Code requirements.

CPHS Administrator

Selection and Appointment

The CPHS Administrator is selected by the Director of CDII with input from the CPHS Chair and/or Vice Chair or assigned CPHS Board Member. The CalHHS Secretary, as the designated Institutional Official on the FWA, approves the designation of the Human Protections Administrator (HPA) on the FWA.

Duties and Responsibilities

1) Serves as the Human Protections Administrator on the CPHS FWA.

2) Assures that CPHS operates in accordance with the terms of the FWA and is in compliance with the Civil Code (shared responsibility with the Chair).

3) Serves as the primary liaison between CPHS members and the federal agencies (e.g., OHRP, FDA), Investigators, and CalHHS officials.

4) Prepares Secretary's Action Requests (SARs) for membership nominations, and other actions needing CalHHS Secretary's approval.

5) Assists Researchers in the preparation and submission of research applications for CPHS review.

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6) Reviews research applications prior to distribution to CPHS members and notifies Researchers if applications are incomplete.

7) Obtains verification of information about projects from sources other than the Researcher at the direction of the Chair.

8) Assigns primary reviewers to project proposals submitted for initial review, in consideration of members' areas of expertise, workload, and conflicts of interest. (Shared responsibility with the Chair and Vice Chair).

9) Provides materials to CPHS members as needed.

10) Works with the Contractor to maintain and improve the IRB electronic system to meet CPHS' workflow requirements, tracks protocols and generate reports.

11) Organizes logistics for all CPHS meetings.

12) Assists in preparation of minutes for CPHS meetings.

13) Prepares CPHS correspondence to Researchers.

14) Reviews requests for exemptions in collaboration with the CPHS Chair and/or Vice Chair

15) Supervises the CPHS administrative staff performs the daily operations and supports the continuous functioning of the CPHS.

16) Maintains the CPHS website.

17) Conducts or arranges educational seminars for Researchers (shared responsibility with the Chair and/or Vice Chair).

18) Informs primary reviewers of concerns expressed by other members regarding research proposals.

19) Approves expense reimbursements for CPHS members, in accordance with CalHHS Rule, under the supervision of the Director of CDII.

CPHS Staff

CPHS Staff are responsible for the following activities as they relate to the HRPP:

1) Preparing and maintaining adequate documentation of CPHS activities.

2) CPHS members (including consultants) are provided with and review submissions (e.g., initial, renewal) to determine whether the proposed research fulfills the criteria for approval.

3) Pre-reviewing all submissions for completeness and evaluating the expertise needed for member review.

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4) Reviewing administrative modifications according to CPHS policy.

5) Ensuring quorum is maintained during CPHS meetings.

6) Taking minutes during convened board meetings and distributing draft versions to CPHS Chairs and others as deemed appropriate.

7) Ensuring meeting minutes are compliant with OHRP/FDA guidance including attendance of members and others present during meetings; actions taken by CPHS; the vote on agenda items including the number of members voting for, against, abstaining or recusing; the basis for the IRB requiring changes to secure approval of research or disapproving research; and any controverted issues and their resolution.

8) Corresponding with researchers, articulating required modifications to study documentation, including informed consent forms, and requesting additional information needed before resubmitting for further review.

9) Participating in training and educational activities on human research protections that are presented to researchers and administrators.

10) Providing guidance to researchers and administrators on the use of the electronic submission system used by CPHS to manage applications for review and automate correspondence.

11) Maintaining evolving laws, regulations, policies, and ethical norms that are applicable to human research activities on the CPHS website.

Conflict of Interest of IRB Members, Chairs, Consultants and Staff

A CPHS member shall not participate in the review process for any project, except to provide information requested by CPHS, in which they have a present, potential or perceived conflict of interest (COI), including any personal, professional, or financial conflicts. Members should notify the CPHS Chair of the COI and should be absent from the meeting room during the discussion and voting phases of the deliberations, except to provide information requested by the CPHS.

Real or perceived COI on the part of any individual conducting research with human participants or responsible for the protection of human participants in research can seriously undermine the credibility of the process and must be avoided. CPHS strives to avoid COIs when performing its obligations.

A COI may take many forms but arises when an IRB member, staff member, or consultant, in relationship to an outside organization, is in a position to influence the research in ways that could lead directly or indirectly to financial gain for the IRB member, IRB staff, or consultant (or their families) or give improper advantage to others, to the detriment of the research.

CPHS members, consultants, or IRB staff will not be assigned to review a research study if they (and/or their spouse, domestic partner, or dependents):

1) Are the principal investigator or another member of the study team.

2) Have a significant financial interest in the research (as defined by policy).

3) Have other personal or professional conflicts that might hamper their ability to perform an impartial review (e.g., are related to the investigator).

No IRB member, including the Chair(s), shall be assigned to review a research study if the member or a member of his or her immediate family has a COI. No CPHS member, including the Chair(s), shall participate in the investigation of actual or alleged noncompliance or other misconduct (other than to cooperate with the investigation) if the member has a conflict as described above.

Prior to the convened meeting, the CPHS Chair will determine if any COI exists on any research that is to be reviewed, and if identified, the IRB administrator will note the conflict on the agenda. No CPHS member, including the Chair(s), may be present for, participate in the deliberations of, or vote on any research for which the member has a conflict as described above. The members may, however, be invited by CPHS to provide information relevant to the board's consideration of the submission.

Meetings

CPHS meets on the first Friday of even-numbered months (February, April, June, August, October, and December) from 8:30 a.m. until the meeting agenda items are completed. Additional meetings may be scheduled, and meetings may be rescheduled or canceled upon determination of the Chair and with appropriate public notice.

Open Meeting Act

Meetings are conducted in compliance with the Bagley-Keene Open Meetings Act. Copies of all materials are distributed to members and discussed at the meeting. Board materials must be available for public viewing. The agenda must be posted at least ten (10) calendar days before the meeting and cannot be changed less than ten (10) days before the meeting except in extraordinary circumstances as permitted by the Bagley-Keene Open Meetings Act.

Quorum

1) In compliance with the Bagley-Keene Open Meetings Act, a quorum is defined as in-person attendance by more than 50% of members. At least one of the members attending in-person or remotely must have primary concern and expertise in non-scientific areas. If quorum will not be present on the date of the convened meeting, the CPHS Administrator will select an alternate Friday to convene the meeting. This alternate date must be before the expiration of project approvals.

2) When reviewing FDA-regulated research, at least one Medical Doctor (MD or DO) must be in attendance.

3) The CPHS Chair, with support from the CPHS Administrator and staff, will confirm that quorum has been met before calling the meeting to order. The CPHS Chair, with support from the CPHS Administrator, assumes the responsibility to ensure that convened IRB meetings maintain quorum during review and deliberation.

4) CPHS members must only vote to make review determinations when a quorum is present; accordingly, the CPHS Administrator will document the votes in the convened meeting minutes.

5) The CPHS Administrator and staff records both arrivals and departures of all members; the CPHS Administrator and staff must notify the CPHS Chair if quorum is not present.

6) If quorum cannot be maintained, the proposed research being reviewed must be deferred to a subsequent meeting and the meeting must cease.

7) Board decisions on research can only be made if the majority of the voting members agree on the decision. Members who abstain remain part of the quorum.

8) CPHS members who have disclosed a personal, professional, or financial conflict of interest with a study must recuse themselves from participating in the meeting as an IRB member (and would become a member of the public) and therefore would not vote on the study.

9) If CPHS members recuse themselves because of a conflict of interest, they cannot be counted to fulfill quorum requirements.

10) Recused CPHS members (who have stopped participating as an IRB member and become members of the public) are not counted among those who vote or abstain from voting.

Proceedings

1) CPHS meetings are conducted in accordance with the Bagley-Keene Open Meeting Act, Robert's Rules of Order, and all federal and state requirements.

2) Meetings are open to the public and recorded.

3) Researchers may arrange to appear before CPHS remotely by contacting CPHS Administrator at least three (3) working days before the meeting.

4) The CPHS Chair calls the meeting to order (the Vice-Chair assumes this responsibility in absence of the Chair) and a quorum count is taken.

5) Researchers are requested to provide CPHS with a brief verbal overview of each unanticipated problem, new proposal, or amendment including a brief summary of project background, objectives, a description of human subject population, how the subjects will participate, and any potential risks and steps taken to minimize those risks. Following the overview from the Researchers, Committee members may ask questions. If no questions arise or once questions are answered, deliberation and vote will proceed. Researchers may leave the meeting for deliberation or once their project review is complete.

6) Primary reviewers discuss concerns they have about each project, followed by a discussion of concerns by other CPHS members.

7) The primary reviewer, or other committee member, presents a motion for action on the proposal. All motions for approval or approval pending minor revisions, must designate a time interval, based on project risk, for approval, but not to exceed one (1) year. A motion must be seconded by another CPHS member before it can be called to a vote.

    a. A motion represents a proposed action by CPHS; members are voting on the motion made before the committee and not on the research protocol, investigator, institution, or sponsor. Examples of motions include: approval, approval with conditions, and other motions

included in this policy document.

b. If a motion fails, this does not represent that CPHS has disapproved the study, rather it indicates that CPHS has not approved the motion. As such, a member needs to put forth a new motion for consideration. This would continue until the item is either tabled (removed from the agenda for further action until a future meeting) or a motion for board action is passed.

c. When voting, members should consider whether the proposed motion is supported by the information presented and whether the applicable regulatory requirements have been satisfied.

d. Motions should clearly identify:

   i. The action proposed;

   ii. Any required determinations (i.e., waiver of informed consent);

   iii. Any conditions required before approval may be finalized; and

   iv. Any required follow-up actions.

e. Members may vote in favor (yes), opposed (no), and abstain. If a member votes yes, that indicates the member supports the motion currently under consideration. If a member votes no, that indicates that the member does not support the motion currently under consideration and may request that the basis for their objection be reflected in the meeting minutes (but this is not required). If a member abstains, that indicates the member has chosen not to vote in favor or against the motion. Members who abstain remain counted in quorum, continue to be considered present for the meeting, and will be recorded as abstaining.

8) Approval of a motion requires a "yes" vote by a majority of CPHS members present (either in-person or remotely) who have not abstained. A member having made a motion cannot vote against their own motion. Motions receiving a tie vote do not pass.

   a. Examples of motions that pass or fail:

      i. If 10 members are voting: 6 vote yes, 2 vote no, and 2 abstain, the vote passes because a majority of members voted yes.

      ii. If 11 members are voting: 4 vote yes, 5 vote no, and 2 abstain, the vote fails because more members voted against the motion than in favor.

      iii. If 10 members are voting: 4 vote yes, 2 vote no, and 4 abstain, the vote passes because 4 of 6 members voting (a majority) supported the motion.

9) Researchers will be informed of CPHS decisions at the meeting (if they are still in the (virtual) meeting room) and in writing within 15 working days after each meeting.

10) Researchers are expected to forward copies of CPHS approval notifications to departments requesting such copies. CPHS does not routinely forward copies of notifications to department

staff unless they are serving as Researchers for the project.

Meeting Minutes

All pages of the minutes should be numbered, include a label (e.g., “CPHS Minutes” in page header), and date of the meeting. Electronic versions of the approved minutes are kept on the shared drive. Copies of relevant sections of the approved minutes are placed in each project’s file. Copies of approved minutes may be requested from CPHS staff. Minutes shall document the following:

1) Date and location of the meeting, including the time the meeting was called to order and by whom.

2) Satisfaction of quorum requirements (number of members needed, number of members present, and presence of at least one non-scientific member).

3) Identity of: members present, members absent, members present with special population expertise (e.g., prison advocate or staff), and CPHS consultants. Scientist, non-scientist, and invited guests will be identified and will include the method by which the Committee member participated (e.g., in person, by phone, or by videoconference). Members who are absent from the meeting will also be noted. If a member leaves the meeting due to a conflict of interest, this will be noted for the specific agenda item with which the member was in conflict.

4) Identity of all other individuals in attendance and participating in the meeting.

5) Summary of announcements and policy discussion.

6) Summary of discussion and vote count to approve minutes from the previous meeting.

7) Individual submission information:

    a) Project title

    b) Project number

    c) Researcher

    d) Basis of Review (Common Rule and/or Civil Code section 1798.24(t))

    e) Primary reviewer

    f) Representatives present to discuss the project, if different from meeting attendance.

    g) Summary of the project and/or proposed revisions

    h) Summary of controverted issues discussed by the CPHS and their resolution.

    i) Basis for requiring changes in or disapproving research.

    j) Motions and CPHS decision, including votes in favor, opposed, abstentions, and members absent at the time of vote (e.g., Total= 13; In Favor-12, Opposed-1, Abstained-0).

k) Degree of risk

l) Review interval

m) Compliance with requirements for waiver of informed consent, if applicable.

n) Compliance with special protections for vulnerable populations, if applicable. Compliance with requirements for waiver of patient authorization under HIPAA, if applicable.

8) Documentation of determinations of Significant Risk or Non-significant Risk for medical devices (for FDA regulated research only).

9) Details of projects reviewed and approved by expedited review since last meeting, including title, PI, approval date, and other pertinent information

10) Number of projects exempted from CPHS Common Rule review since last meeting.

11) Number of other items

12) Time of adjournment

Appeals of Decisions

Researchers may request appeal of decision made by the CPHS Administrator in his/her capacity as a reviewer by contacting the CPHS Chair. Decisions made by the CPHS Chair or individual members in the course of expedited review can be appealed to the full committee. Researchers may request an appeal to the full committee by contacting the CPHS Administrator. If CPHS has disapproved research, these determinations cannot be altered by the CalHHS or other IRBs. All appeals must be made in writing within 60 days of the determination by CPHS. Appeals should describe the rational for the appeal and contain any supporting documentation/justification to be considered. Appeals will be acknowledged by the recipient within one (1) week of receipt. Investigators appealing CPHS decisions should expect to receive information regarding any further consideration by CPHS within 60 days.

Records Management and Retention

All protocols and other project documents submitted for formal CPHS review are maintained in project files in the electronic system in reverse chronological order. Each page of project documents reflects the date/version of the document. All project files and correspondence will be retained by CPHS consistent with CDII's retention policy and state requirements.

In accordance with HHS regulations, IRB records and all study related materials maintained by investigators should be retained for at least three (3) years after the completion of the study. Research that is governed by the FDA requires records to be maintained for two (2) years following marketing approval of the investigational product or two (2) years after the investigation is closed (i.e., the IND application has been withdrawn). For research that involves protected health information, the HIPAA Privacy Rule requires records be retained for at least six (6) years.

CPHS membership records are maintained by CPHS staff in accordance with 45 C.F.R. part 46.115.

Initial Review of Human Subjects Research

Research studies involving human participants must fulfill defined regulatory criteria (45 CFR 46.111; 21 CFR 56.111) before PIs may perform any research activities. CPHS reviews and approves research studies that propose to enroll human participants. There are four types of IRB review:

1) Exempt
2) Limited IRB review
3) Expedited review and
4) Full board review

For each type of review, the primary responsibility of CPHS is to ensure that research participants are protected from experiencing undue risk and from being deprived of their personal rights.

Exempt Review

This policy sets forth both the criteria and process to review research eligible for exempt determinations. CPHS must determine whether research qualifies as exempt; investigators do not make exempt research determinations.

Even if research qualifies for exemption, the research still must adhere to the CPHS' ethical standards, this policy, and research training requirements.

CPHS utilizes a checklist review method to ensure that human participants will be protected while participating in research. The checklist contains the categories for exempt research and other specific requirements for exempt research.

Research Categories Eligible for Exempt Determinations

As per 45 CFR 46.104(d), for research to qualify as exempt, the research (as a whole) must satisfy one or more of the following regulatory categories:

Category 1: Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

a) ***Commonly accepted educational settings*** traditionally imply schools. Educational settings may have a broader meaning, one that accounts for learning environments in which adults, clients, patients, professionals, or teachers commonly receive education.

b) ***Research participation*** must not be a condition of the learning environment or any course curricula. Students and learners should retain the right to refuse to take part in research without sacrificing their standing in educational setting.

Category 2: Research that includes only interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

1) The information obtained is recorded by the investigator in such a manner that the identity of the human participants cannot readily be ascertained, directly or through identifiers linked to the participants; or

2) Any disclosure of the human participants' responses outside the research would not reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, educational advancement, or reputation.

Category 3: Research involving benign behavioral interventions, as defined below, in conjunction with the collection of information from an adult participant through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

1) The information obtained is recorded by the investigator in such a manner that the identity of the human participants cannot readily be ascertained, directly or through identifiers linked to the participants; or

2) Any disclosure of the human participants' responses outside the research would not reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, educational advancement, or reputation.

Benign behavioral interventions are brief, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the participants, and the investigator has no reason to think the participants will find the interventions offensive or embarrassing.

1) Examples of benign behavioral interventions that qualify for exemption include having participants play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

2) If the research involves deceiving the participants regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research. The final rule allows this type of research to occur without the requirements of informed consent because the intervention is not likely to result in harm or offense to the subject, and the subject must prospectively agree to the intervention and the data collection.

    a) CPHS reviews all research involving deception either by expedited review procedures or by the convened IRB.

Category 4: Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

1) The identifiable private information or identifiable biospecimens are publicly available;

2) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human participants cannot readily be ascertained directly or through identifiers linked to the participants, the investigator does not contact the participants, and the investigator will not re-identify participants; or

3) Research studies that involve HIPAA-regulated information or data will be reviewed in accordance with HIPAA Privacy Rule for research.

4) The research is conducted by, or on behalf of, a federal department or agency using government-generated or government-collected information obtained for non-research activities, and conducted in compliance with 45 CFR 46.104(d)(4)(iv).

Category 5: Research and demonstration projects that are conducted or supported by a federal department or agency, or otherwise subject to the approval of department or agency heads, or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine:

1) public benefit or service programs;

2) procedures for obtaining benefits or services under those programs;

3) possible changes in or alternatives to those programs or procedures; or

4) possible changes in methods or levels of payment for benefits or services under those programs.

Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

Category 6: Taste and food quality evaluation and consumer acceptance studies, if at least one of the following criteria is met:

1) wholesome foods without additives are consumed, or

2) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration (FDA) or approved by the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service of the U.S. Department of Agriculture (USDA).

Categories 7 & 8 do not apply to research reviewed by CPHS.

Regulatory Limitations on Exempt Research Involving Vulnerable Populations

1) ***Children***. For research involving children, category 2 only applies to studies involving educational tests and observations of public behavior when investigators **do not** participate in the activities being observed. If investigators engage with children, or if the research involves surveys or interviews, category 2 cannot be utilized. In addition, research with children involving benign interventions (category 3) does not qualify for exemption. All other exempt categories may be utilized for research involving children.

2) ***Prisoners***. Research that proposes to enroll prisoners may not qualify for exemption (45 CFR 46.301(a)), except when the research intends to involve a broader enrollment population of which prisoners would only be enrolled incidentally in the research.

3) ***Other defined vulnerable populations***. The CPHS will review whether research activities may qualify for exemption when they intend to enroll individuals who are cognitively impaired or economically or educationally disadvantaged. The CPHS maintains final authority to determine a study's eligibility for exempt status in regards to proposed participant's vulnerable status.

Procedures for Exempt Review

1) Investigators must complete and submit an exempt initial submission in the CPHS electronic submission system. In the submission, investigators should describe the:

   a) research purpose

   b) research procedures and methodology

   c) risks and benefits; and

   d) confidentiality of research data and provide supporting documents as relevant (e.g., consent forms, recruitment materials, surveys).

2) The CPHS staff ensures that reviewers do not have a conflict of interest.

3) The CPHS staff assigns research to the CPHS Chair or other designated IRB reviewers with appropriate scientific, scholarly, regulatory, or other expertise, to conduct a review of the submission.

4) CPHS Chairs or designated CPHS reviewers are authorized to review requests for research to be exempt, including those research activities that require limited IRB review as a condition of exemption.

5) CPHS Chairs or designated CPHS reviewers will evaluate requests for research to be exempt and determine whether it satisfies the categories for exemption, and whether

adequate provisions have been made to protect both the privacy of human participants and maintain the confidentiality of the data to be collected.

6) CHPS IRB Chairs or designated CPHS reviewers will document applicable exempt categories on the IRB reviewer checklist.

7) Determinations of exempt research are documented and archived in the IRB electronic system.

8) CPHS Chairs or designated CPHS reviewers are also authorized to request clarifications or modifications or to refer research to be reviewed by expedited or full board procedures.

9) During their reviews, CPHS Chairs or designated CPHS reviewers determine whether additional measures or safeguards should be established to protect the rights and welfare of the research participants.

10) CPHS IRB will issue a determination letter, and if approved as exempt, the applicable exempt category will be documented.

11) Researchers must not begin research or perform research procedures (this includes collecting any data intended for research purposes) until the CPHS has issued the determination letter.

12) When the CPHS has granted an exempt determination, investigators are required to submit any substantive proposed changes to their research via an amendment request so the CPHS can review the study as modified and ensure that the research still qualifies to be exempt according to the regulatory criteria. Minor changes do not require submission to CPHS for additional review. Further detail on the definitions of substantive and minor changes is contained in the Amendments policy.

Possible Determinations for Exempt Review

The CPHS determinations made during initial review of research meeting the criteria for exempt review comprise the following:

1) **Acknowledged**: Acknowledged by the CPHS as exempt without explicit conditions. The research may proceed.

2) **Modifications Required**: CPHS requires additional substantive clarification(s) regarding the proposed research; the research lacks sufficient information and the CPHS cannot establish whether it meets the criteria outlined above for an exempt determination to be issued. The research may not proceed until CPHS has acknowledged a revised application incorporating all necessary information.

3) **Not exempt**: Acknowledged by the CPHS as not being eligible for exempt review such that a new submission within the electronic system must be submitted for not regulated, not human subjects research, expedited, or full board review to the CPHS.

Limited IRB Review

Limited IRB review is a type of review that must be conducted to deem certain research exempt. The CPHS uses expedited review procedures to conduct initial limited review of certain exempt research. Limited IRB review is conducted either by the CPHS Chair or an experienced CPHS member designated by the CPHS Chair. Limited IRB review is not recognized by FDA as an eligible review category and therefore, FDA regulated research cannot be reviewed in this capacity.

1) Under limited review, an IRB does not consider all the IRB approval criteria under 45 CFR 46.111; rather, IRB review is limited to determining whether certain conditions are met.

2) Limited IRB review is required to be conducted, as described in the regulations for the protection of protection of human participants at 45 CFR 46.104:

    a) For research that only includes interactions involving educational tests, survey or interview procedures, or observation of public behavior when the information obtained is recorded by the investigator such that the identity of the subjects can readily be ascertained either directly or through identifiers. (45 CFR 46.104(d)(2)(iii)); or

    b) For research involving benign behavioral interventions in conjunction with specified data collection methods when information obtained is recorded by the investigator such that the identity of the subject can readily be ascertained either directly or through identifiers. (45 CFR 46.104(d)(3)(i)(C)).

    c) When reviewing research meeting the criteria for limited review, the CPHS is required to determine that there are adequate provisions in place to protect the privacy of participants and maintain confidentiality of the data.

    d) If the CPHS finds that adequate provisions are in place, the study can be deemed exempt. Conversely, if the CPHS finds that adequate provisions are not in place, it may require changes to the research before the CPHS deems the research to be exempt. If the changes are not implemented, or cannot be implemented, the CPHS Chair or reviewer will refer the research to be reviewed either through expedited procedures or the convened IRB.

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Expedited Review

This policy sets forth both the criteria and process for the initial review of research involving human participants reviewed under expedited procedures (45 CFR 46.110). In accordance with federal regulations, the CPHS uses expedited review procedures to conduct initial review of minimal risk research that satisfies certain criteria (see Research Categories Eligible for Expedited Review).

1) CPHS may review research activities through expedited review procedures when those research activities:

    a) Present no more than *minimal risk* to human participants;

    b) Describe reasonable and adequate protections so that privacy risks and breaches of confidentiality are no greater than minimal, if the identification of the participants or their responses will not reasonably place them at risk of criminal or civil liability or be damaging to their financial standing, employability, insurability, reputation, or be stigmatizing;

    c) Consist only of procedures detailed in one or more of the defined categories in the regulations at Federal Register (FR) Volume 63, No 216; and

    d) Involve research for which limited IRB review is a condition of exemption under 45 CFR 46.104(d)(2)(iii); 45 CFR 46.104(d)(3)(i)(C)

2) The CPHS Administrator, CPHS staff, or any IRB member maintain the authority to refer any minimal risk study submitted to the CPHS which could qualify for expedited review to the convened IRB. This may be done for any reason but may include:

    a) the study includes a particularly vulnerable populations, complex ethical issue, or requires appropriate safeguards and review by the convened IRB may be more appropriate; and/or

    b) the CPHS Administrator, CPHS staff, or any IRB member request review by the convened IRB to obtain public input.

Research that **cannot** be reviewed by expedited procedures include:

1) classified research involving human participants. Classified information is official government information which has been determined to require protection against unauthorized disclosure in the interest of National Security.

2) research requiring a device risk determination.

Initial review of minimal risk research must be consistent with the regulatory criteria to approve research involving human participants (45 CFR 46.111).

CPHS members receive reports at the convened IRB meeting apprising them of each research study that was approved through expedited review procedures (45 CFR 46.110(c)), which includes the:

1) IRB submission number
2) Research study title
3) Name of PI

CPHS members are expected to submit their expedited review within two (2) weeks of receipt of the project proposal.

CPHS utilizes a checklist review method to ensure that human participants will be protected while participating in research. The IRB reviewer checklist incorporates the regulatory criteria to review and approve/re-approve research involving human participants. The checklist assures that the regulatory criteria have been fulfilled and where applicable, it also contains other requirements to approve proposed research.

Research Categories Eligible for Expedited Review

For research to qualify as expedited, the research (as a whole) must satisfy one or more of the following regulatory categories:

1) **Category 1**: Clinical studies of drugs and medical devices only when condition (a) or (b) is met:
    a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
    b) Research on medical devices for which (i) an investigational device exemption application (21 CFR 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2) **Category 2**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
    a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these participants, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; **or**
    b) From other adults and children, considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.
3) **Category 3**: Prospective collection of biological specimens for research purposes by noninvasive means.
    a) Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta

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

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

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

5) **Category 5**: Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

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

7) **Category 7**: Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Procedures for Expedited Review

1) Investigators must complete and submit an initial submission in the CPHS electronic submission system. In addition, investigators should describe the:

    a) research purpose;

    b) research procedures and methodology;

    c) risks and benefits; and

d) confidentiality of research data and provide supporting documents as relevant (e.g., consent forms, recruitment materials, surveys).

2) CPHS staff conducts an administrative review of new studies utilizing a checklist to assess and determine if the proposed research study qualifies expedited review.

3) CPHS utilizes a primary and secondary reviewer system.

   a) CPHS staff evaluates and assigns the application, as closely as possible, to primary reviewers and secondary reviewers whose scientific or scholarly expertise align appropriately to conduct a review of the research. CPHS staff ensures that at least one CPHS member knowledgeable about or experienced in working with the vulnerable participants will be assigned to review the proposed research. CPHS members will not be assigned to review proposed research if they have a personal, professional, or financial conflict of interest with the research. The CPHS staff assures that reviewers do not have a conflict of interest.

4) Research cannot be approved unless both the primary and secondary reviewers agree.

5) Research cannot be disapproved using expedited review procedures; such applications must be referred to the convened IRB for review at its next convened meeting.

6) CPHS reviewers will document applicable expedited categories on the IRB reviewer checklist.

7) Research that has been approved through expedited review procedures receive an approval date the day CPHS reviewers grant approval.

8) Researchers will receive the CPHS approval letter, in which the applicable expedited category will be documented, within one week of approval.

9) Researchers must not begin research or perform research procedures (this includes collecting any data intended for research purposes) until CPHS has issued the approval letter.

10) Renewal of research is not required for research projects initially approved by expedited review, if not FDA regulated. Such research will not be given an expiration date but must submit a closure report the delineates the destruction of protected data.

Possible IRB Determinations for Expedited Review

CPHS determinations made during initial review of research meeting the criteria for expedited review comprise of the following:

1) **Approved**: Approved by the CPHS as written without explicit conditions. The research may proceed.

2) **Minor Stipulations**: The CPHS has determined that research is approved with required minor changes, or stipulations, or pending letters of intent from schools, other research sites, or organizations.

a) Minor changes that are required will be clearly delineated so that the PIs understand CPHS's stipulations and can address them fully.

b) Before any research begins, the PIs must address and complete the stipulations to obtain full approval.

3) **Deferred**: The CPHS requires additional substantive clarification(s) regarding the proposed research; the research lacks sufficient information and the IRB cannot establish whether it satisfies the criteria for IRB approval of research (45 CFR 46.111; 21 CFR 56.111). The research may not proceed until CPHS has approved a revised application incorporating all necessary information.

Full Board Review

This policy sets forth both the criteria and process when reviewing initial research proposals that involve human participants and require full board review (i.e. reviewed by the convened IRB).

1) Except when an exempt determination is made or expedited review procedures are applied, the CPHS must review research involving human participants at convened meetings, often referred to as full board reviews or full committee reviews. At the convened meetings, a quorum of the committee must be present.

2) The CPHS utilizes a checklist review method to ensure that human participants will be protected while participating in research. The CPHS reviewer checklist incorporates the regulatory criteria to review and approve research involving human participants. It assures that the regulatory criteria have been fulfilled and where applicable, it also contains other requirements to approve proposed research.

Procedures for Full Board Review

1) Investigators must complete and submit an initial submission in the CPHS electronic submission system. In addition, investigators should describe the:

a) research purpose;

b) research procedures and methodology;

c) risks and benefits; and

d) confidentiality of research data and provide supporting documents as relevant (e.g., consent forms, recruitment materials, surveys).

2) CPHS utilizes a primary reviewer system for convened meetings.

a) CPHS staff evaluates and assigns the application, as closely as possible, to a primary reviewer whose scientific or scholarly expertise aligns appropriately to conduct a review of the research.

3) **Vulnerable Populations**. When assigning reviews, the CPHS staff identifies participant populations likely to be vulnerable to coercion or undue influence.

a) If identified, CPHS ensures that at least one CPHS member knowledgeable about or experienced in working with the vulnerable participants will be assigned to review the proposed research.

4) CPHS members will not be assigned to review proposed research if they have a personal, professional, or financial conflict of interest with the research.

5) If the CPHS cannot identify a primary reviewer who possesses the appropriate scientific or scholarly expertise to review proposed research, then the CPHS Chair will solicit expert consultants who possess the knowledge to perform a thorough review of the proposed research.

6) Expert consultants who review research for the CPHS must disclose any potential personal, professional, or financial conflicts of interest before they conduct their reviews.

   a) Consultants cannot vote and do not count toward quorum for a convened meeting.

7) CPHS members are required to have access to and review the following materials prior to a convened meeting:

   a) IRB submission for new studies;

   b) informed consent document;

   c) parental permission and/or assent form(s);

   d) investigator brochure, as applicable;

   e) recruitment material;

   f) copies of all participant facing materials (e.g., screening/interview scripts, questionnaires, surveys, or similar instruments); and

   g) other materials as relevant (e.g., debriefing forms, documents translated into languages other than English, letters of permission from external sites).

8) In advance of convened meetings, primary reviewers must receive and review the submitted documents sufficiently enough to not only present findings comprehensively but also deliberate productively about the proposed research. Primary reviewers are expected to begin discussions with researchers about questions or concerns at least one week before the convened meeting. Primary reviewers lead the discussions of their assigned reviews at the convened meeting. Primary reviewers assume the responsibility for:

   a) presenting an overview of the research and their findings;

   b) providing an assessment of the research's scientific and scholarly merits;

   c) discussing the risks and benefits of the research;

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d) reviewing the consent process and document, where appropriate; and

e) recommending specific actions that the IRB should take.

Primary reviewers complete the IRB reviewer checklist that describes their assessment of the research.

f) CPHS members in a convened meeting determine whether the proposed research meets the regulatory criteria for initial approval (45 CFR 46.111; 21 CFR 56.111).

g) When CPHS reviewers necessitate them, additional checklists are utilized and required when the CPHS must consider and document additional regulatory requirements to grant approval of research (e.g., research involving devices).

9) Completed IRB reviewer checklists are archived in the electronic CPHS system or through electronic shared storage; The checklists become part of the official electronic record of CPHS review of research involving human participants.

10) All CPHS members should be familiar with the items to be reviewed by the convened board. CPHS members should review the checklists completed by the primary reviewer as well as any reports by consultants, as applicable.

Possible IRB Determinations for Full Board Review

CPHS meeting minutes record the determinations that the convened IRB makes, as well as the votes that support these determinations. Members must vote “yes”, “no” or “abstain.”

Any CHPS IRB member including the Chair may make a recommendation/motion on agenda items being presented at a convened meeting. Members cannot vote against a motion that they have made.

CPHS determinations made during initial review or renewal of research comprise the following:

1) **Approved**: Approved by the CPHS as written without explicit conditions. The research may proceed.

2) **Approved with Minor Revisions**: CPHS has determined that research is approved with required minor changes, or stipulations, or pending letters of intent from schools or other research sites.

a) Minor changes that are required will be clearly delineated so that the PIs understand CPHS’ stipulations and can address them fully.

b) Before any research begins, the PIs must address and complete the CPHS’ stipulations to obtain full CPHS approval.

c) For approvals with stipulations, CPHS Chair(s) and designated CPHS reviewer(s) may approve the proposed research on behalf of the CPHS upon reviewing the PI's response(s) to the conditions.

i) Responses to clarifications that are directly relevant to regulatory criteria for approval of research must be reviewed by the convened IRB.

ii) When the PI has responded appropriately and completely to all stipulations, an approval is granted. The PI will be issued an approval letter indicating the study expiration date.

3) **Tabled**: CPHS requires additional substantive clarification(s) regarding the proposed research; the research proposal/protocol lacks sufficient information and the CPHS cannot establish whether it satisfies the criteria for IRB approval of research (45 CFR 46.111; 21 CFR 56.111). The research may not proceed until the convened IRB has approved a revised application incorporating all necessary information.

   a) CPHS will invite PIs to the convened IRB meeting if CPHS has additional questions concerning the proposed research.

4) **Disapproved**: The convened IRB has determined that the proposed research cannot be conducted.

   a) A disapproval determination may only be rendered at a fully convened IRB meeting.

   b) If a motion to disapprove is made by the convened IRB, the motion must include the reasons for CPHS to disapprove the study and these reasons must be communicated to the PI.

   c) The research activities proposed present risks that outweigh potential benefits; or the research protocol requires significant revisions because it is deficient in several major areas.

   d) The research protocol and/or other supporting documents require complete revision and must be submitted as a new submission.

      i) PIs may request that the CPHS reconsider disapproved research by submitting a written response to the CPHS following the CPHS meeting.

      ii) CPHS may reconsider its original review determination considering new information the PI offers about the proposed research.

IRB Approval and Expiration Dates

1) Research activities that CPHS has approved without explicit conditions have an effective approval starting on the day they are approved; that is, the date the convened CPHS reviewed and approved the proposed research.

2) If the CPHS has approved research activities with explicit conditions, that research will receive a final approval date that is effective on the day CPHS issued approval with the conditions (e.g., the date of the convened meeting).

3) Research approved by the convened CPHS requires renewal of research. The approval period expires based on the date the convened IRB approved the research. The approval period will not surpass 365 calendar days (366 calendar days if approval has been granted during a leap year) from the approval date. In certain instances, the review interval may be sooner than annually if the CPHS determines more frequent review is necessary as noted below.

    a) In some instances, shorter renewal intervals (e.g., semiannually, quarterly, or after a determined subject enrollment number) may be stipulated. The CPHS meeting minutes will document and justify how the convened IRB has determined the review interval.

4) Instances when the CPHS may require shorter continuing review intervals includes:

    a) There is a high degree of risk to participants;

    b) The stage of research is such that many of the risks are unknown;

    c) The proposed procedures have not been used in human participants;

    d) There have been confirmed instances of serious or continuing noncompliance; and

    e) Other reasons for which the CPHS requests closer monitoring.

5) Investigators will be notified in writing of approval and expiration dates for their research. Researchers are encouraged to review determination letters thoroughly and retrieve all newly approved study documents (e.g., informed consent documents, recruitment materials) from the electronic system.

Notification of CPHS Action

1) After CPHS has reviewed the proposed research, the PI will be notified of CPHS's determination in writing within 15 working days after each meeting.

2) For deferred research, the PI will be notified of the reasons the research was deferred. The entire submission, with all required documents, will need to be resubmitted after revision for CPHS review

3) For research that is disapproved, the PI will receive a letter that delineates the reasons for disapproval. PIs may appeal the determination in writing to the CPHS Chair (see section on appeals).

4) Researchers are expected to forward copies of CPHS approval notifications to departments requesting such copies. The CPHS does not routinely forward copies of notifications to department staff unless they are serving as researchers for the project.

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Continuing Review of Research Involving Human Participants

This policy describes when continuing review (or renewal) of research must occur for research that underwent initial CPHS review and approval. In addition, this policy describes the requirements for conducting continuing review of research.

As per 45 CFR 46.109(f)(1) continuing review of research is not required for studies deemed exempt by CPHS or for minimal risk research that was approved by CPHS via expedited review procedures after January 21, 2018, unless CPHS provides a justification for requiring renewal at the time of initial approval.

45 CFR 46.109(e) requires CPHS to conduct a review for renewal of human participants research at intervals appropriate to the degree of risk, but not less than once per year as follows:

1) greater than minimal risk research approved by convened IRB;
2) Food and Drug Administration (FDA) regulated minimal risk research approved by expedited review procedures;
3) minimal risk research approved by expedited review procedures prior to January 21, 2018; and/or
4) minimal risk research approved by expedited review procedures after January 21, 2018, when CPHS documents its decision along with its rationale and interval for annual review.

During the continuing review process, CPHS determines that all regulatory requirements as set forth in 45 CFR 46.111 and 21 CFR 56.111 are met, or continue to be met, as a condition for approving research for continuation.

At the time of continuing review, CPHS may determine which research studies require verification from sources other than the investigator to assure that no material changes in the research have occurred since the previous CPHS review.

CPHS utilizes a reviewer checklist to ensure human participants will be protected while participating in research. The CPHS continuing review checklist incorporates the regulatory criteria to review and approve research involving human participants. The checklist assures that the regulatory criteria have been fulfilled, and where applicable, also contains other requirements to approve research.

Research that Does Not Require Continuing Review

1) As per 45 CFR 46.109(f)(1)(i-iii), research that meets at least one of the following criteria does not require continuing review but is still subject to CPHS oversight:
    a) research was reviewed in accordance with the limited IRB review procedure;

b) non-FDA regulated research is eligible for initial review by the expedited procedure after January 21, 2018;

c) the convened IRB (i.e., the full board) has determined the research presents no greater than minimal risk to participants;

d) the research has progressed to the point that it involves identified data or de-identified data analysis only; and/or

e) the research involves accessing follow-up data from procedures that participants would undergo as part of clinical care.

2) CPHS may determine that research meeting the above criteria is required to undergo continuing review in the following circumstances:

a) The research sponsor is requesting continuing review as a condition of funding;

b) The research involves oversight that must be monitored, such as conflicts of interest for the researchers or institution; and/or

c) The PI or other researchers have had serious non-compliance or a pattern of non-serious non-compliance in their research practice.

When continuing review is required for research meeting the above-referenced criteria, CPHS will specifically document in the electronic system that renewal is required for the research, including the frequency of such review as well as the justification for requiring the continuing review.

CPHS requires investigators to submit an annual administrative check-in application for research that is otherwise not subject to continuing review (as per the criteria above). Although a formal continuing review submission might not be required, PIs continue to be responsible for submitting any unanticipated problems, serious or continuing non-compliance, and modifications to the approved research for the life of the study. Annual check-ins for minimal risk research allow CPHS to stay current on study activities to date and ensure compliance with any requirements imposed on the research. Annual check-ins are essential to assess any newly recognized risks to the research, review protocol changes, and confirm the study remains active.

If a PI fails to submit an annual check-in for a study, CPHS will send a notification to the department of the data owner, CalHHS leadership, and/or the PI's Institutional Official. Failure to submit annual check-ins will result in an administrative closure of the project and may result in sanctions for investigators, including but not limited to disallowance of research applications for review by CPHS in the future. See the Research Noncompliance policy for further information on CPHS review of noncompliance activities.

PIs must notify CPHS of the completion of the research via the Closure Report in the IRB electronic system when research activities, including enrollment, intervention, and analysis of identifiable data, are complete. Failure to submit a closure report to CPHS when research activities are complete will result in an administrative closure of the project and may result in sanctions for investigators, including but not limited to disallowance of research applications for

review by CPHS in the future. See the Research Noncompliance policy for further information on CPHS review of noncompliance activities.

Administrative closure of projects in line with these policy statements do not constitute a termination of research by CPHS.

Notification of Continuing Review

As a courtesy, CPHS will send email reminders to PIs before the research expires. Reminder emails will be sent 90, 60, 45, and 30 days prior to study expiration through the electronic IRB system. However, it is ultimately the PI's responsibility to complete and submit the continuing review application in time for CPHS review and approval prior to the study's expiration of approval.

CPHS recommends investigators submit a continuing review application at least 30 days prior to the expiration of research reviewed by expedited procedures and 60 days prior to the expiration for research requiring full board review. This will allow sufficient opportunity for CPHS or the CPHS Administrator to review the submission and make a determination prior to the expiration date.

Continuing Review of Research Using Expedited Procedures

1) CPHS will use expedited review procedures to conduct continuing review of:
    a) research previously approved via expedited review procedures that continues to be eligible for expedited review.
    b) research previously approved by the convened CPHS where:
        i) the research is permanently closed to the enrollment of new participants, all participants have completed all research-related interventions, and the research remains active only for long-term follow-up of participants;
        ii) where no participants have been enrolled and no additional risks have been identified either at the local site or at any site if the research involves a multi-site study;
        iii) the remaining research activities are limited to data analysis; and/or
        iv) continuing review of research not conducted under an Investigational Device Exemption (IDE) (21 CFR Part 812) where expedited categories two (2) through eight (8) do not apply but CPHS determined and documented at a convened meeting, and in the meeting minutes, that the research is no greater than minimal risk and no additional risks have been identified (Expedited Category 9).

Continuing Review of Research Originally Reviewed by the Convened Board

1) Unless expedited review procedures are applied, CPHS must review research involving human participants at convened meetings.

2) CPHS will review continuing reviews in the same manner it reviews initial submissions.

3) In addition, CPHS will also consider:

   a) any unanticipated problems involving risks to research participants;

   b) any new information regarding the risks and benefits to the research participants;

   c) risks posed by the study procedures (e.g., interventions or interactions with participants);

   d) the type of safety monitoring needed as determined during the initial review; and

   e) changes in the risk to benefit ratio.

CPHS Approval and Expiration Dates

1) When CPHS conducts the initial review, as well as at each renewal, it will determine the interval of continuing review (e.g., 6 months, 1 year). CPHS will evaluate the risks associated with the proposed research to make a determination of a review interval that corresponds with the degree of risk. The approval period will not surpass 365 calendar days (366 calendar days if approval has been granted during a leap year) from the approval date. The rationale for shorter renewal periods is outlined in the Initial Review section of this procedure manual. CPHS meeting minutes will document and justify how the convened committee has determined the review interval.

2) Research activities that CPHS has approved without explicit conditions have an effective approval starting on the day they are approved; that is, the date the convened IRB reviewed and approved the proposed research.

If CPHS has approved research activities with explicit conditions, the project will receive a final approval date that is effective on the day CPHS issued approval with the conditions (e.g., the date of the convened meeting).

1) PIs will be notified in writing of approval and expiration dates for their research. Researchers are encouraged to review determination letters thoroughly and retrieve all newly approved study documents (e.g., informed consent documents, recruitment materials) from the electronic system.

Extensions of the Approval Period

1) There is no grace period extending the research beyond the expiration date of CPHS approval. If CPHS has not reviewed a renewal submission and re-approved the research prior to the study expiration date, CPHS approval automatically expires. If this should occur, the PI must stop all research activity, including but not limited to interactions and interventions with participants, as well as data analysis.

   a) During a lapse of CPHS approval, new participants cannot be enrolled, and prospective data cannot be collected until the continuing review process has been completed.

b) Should an investigator wish to continue the research following the study expiration, a new application may be required to be submitted for CPHS review and approval if the study has been expired for more than 60 days.

Criteria for Continuing Review of Research

1) The criteria for approval of research detailed at 45 CFR 46.111 and 21 CFR 56.111, and all applicable regulatory subparts, are reevaluated during the continuing review process. During review, CPHS board members are provided with and review the following documents:

   a) consent, parental permission, and assent document(s);

   b) continuing review application which includes a summary since the last CPHS review of:

      i) the number of enrolled participants;

      ii) any significant new findings that may relate to the research participant's willingness to continue participation;

      iii) adverse events and adverse outcomes experienced by participants;

      iv) unanticipated problems involving risks to participants or others;

      v) participant withdrawals;

      vi) the reasons for withdrawals;

      vii) complaints about the research;

      viii) modifications;

      ix) any relevant recent literature;

      x) any interim findings;

      xi) any relevant multi-center trial reports; and

      xii) the researcher's current risk to benefit assessment based on study results.

   c) The CPHS Administrator or staff assigns CPHS members to serve as the primary reviewer for each renewal submission.

Possible CPHS Actions

The determinations outlined below are applicable to research reviewed by expedited procedures or the convened committee.

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Approved: Approved by CPHS as written without explicit conditions. The research may proceed.

Approved with Minor Contingencies: CPHS has determined that research is approved with required minor changes.

a) Minor changes that are required will be clearly delineated so that the PIs understand CPHS' stipulations and can address them fully.

b) The PI must address and complete the stipulations to obtain full CPHS approval.

c) For approvals with stipulations, the CPHS Chairs or designated CPHS reviewers may approve the proposed research on behalf of the CPHS upon reviewing the PI's adequate response(s) to the conditions.

d) When the CPHS approves research with minor stipulations prior to the expiration date of the preceding CPHS approval period, CPHS approval does not lapse. Investigators have 30 calendar days following receipt of the stipulations to secure full approval.

Tabled: CPHS requires substantive clarification(s) regarding the proposed research or the research lacks sufficient information and CPHS cannot establish whether it satisfies the criteria for IRB approval of research (45 CFR 46.111; 21 CFR 56.111). The research may not proceed until the convened committee has approved a revised application incorporating all necessary information.

Disapproved: CPHS has determined that the proposed research cannot be conducted.

a) A disapproval determination may only be rendered at a fully convened meeting.

   i) PIs may request that CPHS reconsider disapproved research by submitting a written response to CPHS.

   ii) The CPHS may reconsider its original review determination in light of new information the PI offers about the proposed research

The CPHS meeting minutes record the determinations that the convened IRB makes, as well as the votes that support these determinations.

Amendments at Continuing Review

Researchers may submit an amendment to the research (e.g., changes to personnel, informed consent forms, recruitment materials) simultaneously with continuing review. These are two separate submissions in the IRB electronic system. Investigators must acknowledge in their Continuing Review applications that approval for any proposed changes will be secured prior to being implemented. Investigators must follow the process described in the policy for amendments to research involving human participants.

Notification of CPHS Action

1) After the CPHS meeting at which the research was reviewed for continuing review, the PI will be notified of CPHS' determination.

2) For research reviewed at a convened meeting, CPHS will determine whether the PI's responses to minor stipulations must be reviewed by the convened committee or may be reviewed for appropriateness and completeness by the CPHS Chair or designated reviewers. Responses to clarifications that are directly relevant to regulatory criteria for approval of research must be reviewed by the convened committee.

3) When the PI has responded appropriately and completely to all stipulations, a continuing review is granted. The PI will be issued an approval letter indicating a new study expiration date and stating that the research can continue.

4) For deferred research, the PI will be notified of the reasons the research was deferred. The entire submission, with all required documents, will need to be resubmitted after revision for CPHS review. If CPHS approval expires during the deferral (prior to CPHS approving or approving with minor stipulations), all research activities must cease.

CPHS Review of Amendments

This policy sets forth both the criteria and process to review amendments to research involving human participants, which was approved by CPHS either at a convened meeting or using expedited review procedures. This policy also applies to research CPHS has deemed exempt.

When research involving human participants has already been granted CPHS approval, any changes to the research must not be implemented or initiated without CPHS review and approval, except where necessary to eliminate apparent immediate hazards to human participants.

1) In such cases, the changes to the research must be submitted as an amendment to CPHS within 24 hours following their implementation.

2) PIs must also submit an incident report within 24 hours that outlines the circumstances and rationale surrounding the immediate change. In addition, the deviation submitted must include any documents used to communicate the change to research participants.

When CPHS has conducted a limited-scope review of screening, recruitment, or informed consent activities, study teams must submit amendments to CPHS for review if the changes requested affect any study document or procedure utilized during screening, recruitment, or informed consent processes. Refer to the Authority of CPHS or Informed Consent policy for more information.

Processes related to the review of amendments are as follows:

3) PIs must submit amendments to their approved research through the electronic system using the amendment form.

4) CPHS reviews all changes to approved research and determines whether the research continues to satisfy the regulatory criteria for approval (45 CFR 46.111; 21 CFR 56.111), along with any other applicable review requirements (e.g., institutional, state, departmental).

5) CPHS utilizes checklists to ensure that human participants will be protected while participating in research. When the CPHS Chair and the designated CPHS reviewer(s) consider changes to expedited or full board approved research, they utilize the reviewer checklist for amendments to determine whether the:

   a) Amendments to previously approved research continue to satisfy the regulatory criteria for the approval;

   b) Amendments are related to any significant new findings that might affect research participants' willingness to remain in the study; and

   c) Amendments propose to change the PI, and whether the newly identified PI is qualified with the appropriate background and experience to oversee the research.

6) The CPHS Chair and designated CPHS reviewer(s) are required to receive and review the following documents when they review changes to any previously reviewed CPHS study:

   a) IRB submission amendment form;

   b) revised consent, parental permission, and/or assent documents (if modified);

   c) other materials used with research participants (if modified) including recruitment materials, surveys, interview questionnaires, etc.; and

   d) other documentation pertaining to the proposed amendments to approved research.

Administrative Review of Amendments to Approved Research

1) CPHS authorizes the CPHS Administrator and staff to review and acknowledge certain administrative amendments to approved research including:

   a) Correcting typographical errors, or other similar errors, in the informed consent form or participant recruitment material;

   b) Making minor revisions or updates to contact information for either CPHS or researchers;

   c) Reviewing changes to research personnel except for a change in PI;

   d) Reviewing changes to the number of participants in research deemed exempt; and

   e) Verifying translator credentials when documents have been translated into languages other than English, and when CPHS has previously approved the English version of the documents.

      (1) **Note**: Changes must not have been made to the previously IRB-approved versions of the translated documents that are reviewed administratively.

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Amendments of Exempt Research

1) Investigators are required to submit any substantive proposed changes to their research via an amendment so CPHS can review the study as modified and ensure that the research still qualifies to be exempt according to the regulatory criteria. Minor changes do not require submission to CPHS for additional review.

    a) Substantive changes: these are changes to existing exempt studies which may affect the exempt status of the study or include new information for which CPHS must be notified, including (but not limited to):

        i) Changing the PI;

        ii) Changing the funding source;

        iii) Changing the study purpose or procedures (including adding new methods, adding a new survey, new source or method of data collection, etc.);

        iv) Changes to the study population targeted for recruitment or analysis;

        v) Changing the identifiability status of the research data received or recorded;

        vi) Changes which may affect the risks involved in the study; or

        vii) Increasing the number of participants to be targeted or analyzed in the study.

    b) Minor changes: these are changes to existing exempt studies which will not affect the exempt status of the study or will not include information for which CPHS must not be notified, including (but not limited to):

        i) Changing study staff (other than the PI);

        ii) Editorial changes that clarify but do not alter the existing meaning of a document (e.g., grammatical corrections, wordsmithing, addition of clarifying questions, addition of very similar questions to those previously approved, or deletion of questions, etc.); or

        iii) Minor revisions to recruitment materials or plans (e.g., change to a phone number or using existing materials in a new methodology like bus ads put into a newspaper).

2) The CPHS Chair or Vice Chair must assess any amendments requested for exempt research to determine whether the changes would alter, in any way, the original exempt determination.

3) The CPHS Chair or Vice Chair must determine whether changes in exempt research would disqualify the research from exempt status. When changes alter the research in such a way that it is not eligible for exemption any longer, the research then requires review and approval either through expedited review procedures or full board review.

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Expedited Review of Amendments to Approved Research

1) CPHS is authorized to review minor changes to previously approved research using expedited review procedures. The CPHS Chair and designated CPHS reviewer(s) may conduct expedited reviews and determine whether the research, as modified, continues to satisfy the regulatory criteria for approval (45 CFR 46.111; 21 CFR 56.111).

    a) **Minor Changes** are those that do not alter the:

        i) level of risk to participants;

        ii) research design or methodology substantially;

        iii) number of participants enrolled in the research;

        iv) qualifications of the research team; and

        v) facilities and resources available to support the safe conduct of the research

2) Changes to research originally eligible for expedited review can continue to be reviewed through expedited procedures, unless the changes alter the study in such a way that the research is no longer eligible for expedited review. In this case, the amendment would need to be reviewed by the convened IRB.

Convened Review of Amendments to Approved Research

1) The convened IRB must review changes to previously approved research when those changes are not considered to be minor amendments. In other words, amendments that would potentially increase the risks to or affect the rights, welfare, and safety of research participants will be reviewed by the convened IRB.

CPHS Documentation

1) CPHS will notify researchers in writing of its decision to approve or disapprove amendments to previously approved research. Should CPHS disapprove an amendment, it shall include a statement of the reasons for its decision and give the PI an opportunity to respond in writing.

2) All amendments and the resulting CPHS determinations are maintained in the designated electronic system. Researchers are encouraged to review determination letters thoroughly and retrieve all newly approved study documents (e.g., informed consent documents, recruitment materials) from the electronic system.

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Informed Consent

As per the Common Rule and FDA regulations, researchers may only involve human participants in research when the legally effective informed consent has been obtained from the participant or the participant's legally authorized representative (LAR) (45 CFR 46.116, 21 CFR 50.20). The FDA has also issued guidance that may be helpful when reviewing informed consent documents.

Exceptions to this policy include:

1) Exempt research for which investigators should include an information sheet for participants; and
2) In circumstances where CPHS grants a waiver or modification of the informed consent requirement.
3) Studies that are reviewed under the IPA only

Researchers shall seek prospective informed consent from a participant or LAR after the individual has sufficient opportunity to discuss and consider their participation. Researchers must also minimize the possibility of coercion or undue influence.

Researchers must describe how the informed consent process will be conducted, the setting in which it will occur, how long individuals will have to consider participation, and methods to prevent coercion or undue influence in the electronic IRB system.

Researchers should consider informed consent as a process, not just a form, by which the research study is thoroughly explained to the potential participant. The requirement to obtain informed consent is an ethical obligation. Documentation of informed consent is accomplished with a signed consent form.

If the research involves children and the investigator has not requested, or the IRB has not granted a waiver of alteration of informed consent, permission from a parent (either one or two) and assent of children aged 7 or older must be obtained. (See Policy on research involving vulnerable populations for additional information.)

The following are informed consent requirements:

1) The information that is given to the prospective participant or their LAR (whether orally or in writing) shall be in language understandable to the participant or LAR.
2) The prospective participant or LAR must be provided with the information that any reasonable person would want to have to make an informed decision about whether to participate.
3) The informed consent form must present information in sufficient detail relating to the research and must be organized and presented in a way that does not merely provide lists of isolated facts but rather facilitates understanding of the reasons why one might or might not want to participate.

a) Except in cases where the informed consent document is short enough such that the entire form may be considered key information, informed consent must begin with a concise and focused presentation of the key information that will assist a participant or LAR in understanding the reasons one may or may not want to participate in the research.

4) The informed consent form cannot include any exculpatory language through which the participant or LAR is made to waive or appear to waive any legal rights, or that releases or appears to release researchers, the sponsor, the institution, or its agents from liability for negligence.

   a) In all cases, consent forms must be consistent with applicable state laws and federal regulations. The informed consent requirements stated in this policy are not intended to preempt any applicable federal, state, or local laws that require additional information be disclosed for informed consent to be legally effective.

Use of Data for Screening & Eligibility Purposes

CPHS may approve research in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting or determining eligibility of prospective subjects without informed consent of either the subject or their LAR, if the following conditions are met:

1) The investigator will obtain information through oral or written communication with the prospective subject or LAR; or

2) The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored biospecimens.

However, based on the quantity and sensitivity of the data being collected at screening, CPHS may require prior informed consent. Additionally, screening procedures performed solely in connection with a research protocol to generate diagnostic information (e.g., EKG, Neuropsych testing) is considered part of the research and therefore, informed consent must be obtained prior to the procedures.

Should investigators wish to include screening data collected without the informed consent of subjects in data analysis, the use of the screening data must be outlined in the informed consent form signed by prospective subjects prior to participation in the research If the prospective participant does not sign the informed consent form to participate in the study, screening data cannot be used in the analysis.

CPHS Submission and Review

1) The researchers must describe the informed consent process in the electronic IRB system and provide an informed consent form for CPHS review and approval, when appropriate. CPHS reviews the information and ensures that all requirements consistent with this policy are met.

2) When CPHS review authority is limited to recruitment, screening, and informed consent activities under the Authority of CPHS policy, CPHS review of the informed consent document is limited to evaluating the accuracy, completeness, and appropriateness of

information provided during participant recruitment and enrollment and shall not constitute approval of all study procedures described within the consent document.

3) Upon approval, the informed consent form is uploaded to the electronic system for use by the researchers.

Informed Consent Process

1) Informed consent is an ongoing process of information exchange that provides the prospective participant or participant's LAR with adequate information pertaining to the research study; sufficient opportunity to consider aspects of the research, including the risks and benefits, and whether to participate; and the opportunity to ask questions and receive answers to those questions, thus minimizing the possibility of coercion or undue influence.

    a) To ensure a complete and compliant consent process, it is important that the person consenting be knowledgeable about the research and if relevant, the condition being studied.

2) The informed consent process is often conducted via a conversation between the researcher and the prospective participant or participant's LAR. The informed consent form provides a guide for the conversation and provides the participant or LAR with information that can be referenced later. If the informed consent conversation cannot be conducted face-to-face, the informed consent process may be conducted over the telephone or via other electronic means. In this situation, it is recommended that the participant be provided with a copy of the informed consent form in advance.

3) Participants who can understand and comprehend spoken English but are unable to read the informed consent form for any reason (e.g., illiteracy, blindness or diminished vision, dyslexia) may be enrolled in a study; however, special care must be taken to ensure such individuals are able to understand the concepts of the study and evaluate the risks and benefits of being in the study when it is explained orally.

    a) The study team must present the information orally and document the circumstances.

    b) A witness must observe the entire consent process and sign the consent form.

    c) Technology solutions should be considered to aid in the ability of a research subject to access the information (e.g., electronic consent capabilities, use of accessibility checkers and readability evaluators, utilizing visual aids).

Elements of Informed Consent

1) Informed consent forms must begin with a concise and focused presentation of the key information that is most likely to assist a prospective participant or LAR in understanding the reasons why one might or might not want to participate in the research.

2) Unless altered or waived by CPHS, the following information shall be provided to each prospective participant or LAR who is considering participation in a research study. CPHS may require that additional information be given to participants when, in their

judgment, the information would meaningfully add to the protection of the rights and welfare of participants.

a) A statement that the study involves research, an explanation of the purposes of the research, the expected duration of participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

b) A description of any reasonably foreseeable risks or discomforts to the research participant.

c) A description of any benefits to the research participant or to others that may reasonably be expected from the research.

d) A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the research participant.

e) A statement describing the extent to which, if any, confidentiality of records identifying the research participant will be maintained and for FDA regulated research, notes the possibility that the FDA may inspect the records.

f) For research involving more than minimal risk, an explanation as to whether any compensation is provided and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

g) An explanation of whom to contact for answers to pertinent questions about the research and participants' rights, and whom to contact in the event of a research-related injury to the research participant.

h) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which they are otherwise entitled.

i) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

    i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another researcher for future research studies without additional informed consent from the participant or LAR, if this might be a possibility; or

    ii) A statement that the participant's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

3) The following additional elements shall be provided to each participant or LAR, when appropriate:

    a) A statement that the particular treatment or procedure may involve risks to the research participant (or to the embryo or fetus if the research participant is or may

become pregnant), which are currently unforeseeable (this is usually limited to biomedical research involving clinical treatment or procedures).

b) Anticipated circumstances under which participation may be terminated by the researchers without regard to the participant's consent (e.g., if a participant fails to comply with research procedures).

c) Any additional costs to the participant that may result from research participation (this is usually limited to biomedical research involving billing participants or participants' health insurance for services provided as part of research).

d) The consequences of a research participant's decision to withdraw from the research and procedures for orderly termination of participation by the research participant.

e) A statement that significant new findings developed during the course of the research, which may relate to the participant's willingness to continue participation, will be provided to the participant.

f) The approximate number of research participants involved in the study.

g) A statement that the participant's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the participant will or will not share in this commercial profit.

h) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to participants, and if so, under what conditions (this is usually limited to biomedical research).

i) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen; this is usually limited to biomedical research).

4) The following additional information must be provided in consent forms when applicable:

a) When seeking informed consent for certain clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement notifying the participant that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act: *"A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time."*

b) If research personnel have a conflict of interest related to a research study, a statement regarding the conflict of interest as determined by the Conflict of Interest Management Plan.

c) For studies where a Certificate of Confidentiality has been granted, including any study funded by the National Institutes for Health (NIH), a statement regarding Certificate of Confidentiality protections.

d) If the research involves genetic information, a statement describing the protections provided by the Genetic Information Nondiscrimination Act (GINA) of 2008 and the California Genetic Information Nondiscrimination Act (CalGINA).

e) When seeking informed consent from participants who will participate in a study involving a "medical experiment," investigators must provide participants (or LARs) with a copy of the "Experimental Participant's Bill of Rights" along with a study specific informed consent form. Participants must be provided with a copy of the Experimental Participant's Bill of Rights form in a language in which the participant is fluent.

   i) A "medical experiment" study includes one or more of the following procedures:

      1. The severance or penetration or damaging of tissues of a human participant or the use of a drug or device, electromagnetic radiation, heat or cold, or a biological substance or organism, in or upon a human participant in the practice or research of medicine in a manner not reasonably related to maintaining or improving the health of the participant or otherwise directly benefiting the participant.

      2. The investigational use of a drug or device

      3. Withholding medical treatment from a human participant for any purpose other than maintenance or improvement of the health of the participant.

   i) When the Experimental Participant's Bill of Rights is provided to participants, the following statement should be included: "*You have been given a copy of this form to keep."*

   ii) Participants need not sign the Experimental Participant's Bill of Rights form; however, a research team member should document that each participant received the form.

Documentation of Informed Consent

1) Informed consent is documented by the use of an approved, written consent form described in 21 CFR 50.25 and 45 CFR 46.116(a), that is signed and dated by the prospective participant or LAR at the time of consent.

2) Unless the CPHS grants a waiver of documentation of informed consent, informed consent must be documented as follows:

   a) Participants who are willing to participate in research must sign a copy of the CPHS-approved informed consent form prior to participating in research procedures.

   b) For any federally funded research, participants must only sign a copy of the CPHS-approved informed consent. If the research is FDA-regulated, participants must sign and date the copy of the CPHS-approved informed consent.

      i) Signature may be provided via a physical "wet" signature, a digital copy of a wet signature, verified electronic signature via encrypted digital signature, or electronic signature pad.

ii) If the consent conversation is not conducted face-to-face, the participant may fax, email, or mail a signed copy of the informed consent form to the researcher.

3) Unless CPHS approves otherwise, the study team must receive a copy of the signed informed consent form prior to beginning research procedures.

4) If participants are physically unable to provide a signature, they can make a mark on the informed consent form, and the researchers must document the circumstances. If participants are unable to make a mark, a witness must observe the documentation process and sign the consent form as the witness to the consent process.

5) For FDA regulated research involving greater than minimal risk, the person conducting the consent discussion must also sign and date the informed consent form as the "person obtaining consent.

6) The signature of the principal investigator is not required unless they are the person conducting the consent discussion.

7) Research personnel shall give either the participant or LAR adequate opportunity to read the informed consent form before it is signed, or alternatively this form may be read to the participant or LAR.

Waiver of Documentation of Informed Consent

1) CPHS may waive the requirement for researchers to obtain a signed informed consent form for some or all participants if CPHS determines at least one of the following criteria are met:

   a) That the only record linking the participant and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant or LAR is asked whether they want documentation linking themselves with the research, and the participant's wishes govern.

   b) That the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.

      i) This is the only criterion that CPHS may use to waive the requirement that the participant or LAR sign a written consent form for Food and Drug Administration (FDA) regulated research.

   c) If the participants or LARs are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to participants and if there is an appropriate alternative mechanism for documenting that informed consent was obtained.

2) In cases in which the documentation requirement is waived, the consent process must include all elements listed in the Elements of Informed Consent section of this policy unless CPHS issues an alteration of informed consent. Justification for the waiver must be outlined in the electronic IRB system. CPHS may require researchers to provide participants or LARs with a written statement regarding the research (i.e., an information

sheet).

Waiver or Alteration of Consent

1) CPHS may waive the requirement to obtain informed consent in its entirety, or approve a consent procedure that omits or alters some of the elements of informed consent if the CPHS determines all of the following criteria are met:

   a) The research involves no more than minimal risk to the participants.

   b) The research could not practicably be carried out without the requested waiver or alteration.

   c) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable manner.

   d) The waiver or alteration will not adversely affect the rights and welfare of the participants.

   e) Whenever appropriate, the participants or LARs will be provided with additional pertinent information after participation. (This criterion is specific to research involving deception.)

2) The FDA has adopted the same criteria for waiving or altering informed consent for FDA regulated research (see 21 CFR 50.22).

3) Investigators must justify their request to waive or alter some or all the elements of informed consent in the electronic IRB application. In addition, CPHS must find and document that a study satisfies all waiver criteria.

Informed Consent Procedures for Participants Who Cannot Read English

1) The consent conversation and informed consent form must be in a language understandable to the participant (e.g., in the participant's first language or a language in which the participant is fluent).

2) If researchers plan to enroll non-English-reading individuals, plans for language-appropriate consent procedures must be described in the electronic IRB submission.

3) If a non-English informed consent form is provided for CPHS review and approval, CPHS requires a certificate of translation attesting to the fact that the translated documents are complete and accurate translations of the English version of the informed consent form that is approved by CPHS. In rare cases of demonstrated financial burden, CPHS will consider an attestation of back translation for translated consent documents.

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Informed Consent Procedures involving Surrogate Consent

1) Federal regulations require that consent be sought from a research participant or LAR and defer to "applicable law" to define who is legally authorized (45 CFR 46.116 and 21 CFR 50.20). In California, Health and Safety Code 24178 describes who may serve as a LAR to give consent for an incapacitated prospective research participant.

   In accordance with both federal regulations and California law, the following guidelines must be taken into account when considering whether to enroll participants via surrogate consent methods:

   a) CPHS must specifically approve the use of surrogates in a research study.

   b) The submission must include a process for formal evaluation of the prospective participant's ability to participate in the consent process, unless the prospective participant cannot participate in the consent process (e.g., an unresponsive individual).

   c) If surrogate consent will be sought for a responsive participant, the participant must be told of the researcher's plan to consult a surrogate.

   d) If a participant in any way objects to or resists study participation or the use of surrogate consent, that participant may not be included in the study.

Informed Consent Procedures with Special Populations

1) Certain populations of participants require additional protections regarding their consent to participate in research. Please see applicable CPHS Policies for additional consent requirements when involving these populations in research (e.g., research involving individuals with diminished mental capacity).

Revisions to the Informed Consent Form

1) Revisions to the informed consent form must be reviewed and approved by CPHS prior to implementation.

2) Newly enrolled participants must sign the most recently approved version of the informed consent form, unless CPHS approved the study with waiver of documentation of informed consent. While a copy of the previously approved informed consent must be maintained in the research files, all additional copies should be discarded to prevent inadvertent use by researchers.

3) When submitting a revised informed consent form for CPHS review and approval, the researchers must notify CPHS whether previously enrolled participants will be notified of the new information and, if so, the timing and mechanism of the notification (e.g., email or other written correspondence, telephone). CPHS will consider the researchers' plan for notification and ensure its appropriateness.

4) If the researchers are aware of new or increased risks that are not reflected in the CPHS-approved informed consent form, they must not enroll new participants until the

revised informed consent form incorporating these risks is reviewed and approved by CPHS.

5) If CPHS agrees that previously enrolled participants must be notified of new or different information or re-consented using a new informed consent form, the notification or re-consent process should be documented. Any previously signed consent forms must be retained in the research records and not discarded. Please refer to the institutional records retention policies for more information.

Participants Withdrawn from Research

1) If a participant wishes to discontinue participation in the research, data collected on the participant to the point of the participant's withdrawal from a study typically remains part of the study records.

    a) The Office of Human Research Protections (OHRP) provides guidance on this topic which states that investigators can retain and analyze already collected data related to participants who choose to withdraw from the research or whose participation is terminated by the investigator provided that all analyses falls within the scope of the research approved by CPHS.

    b) The Food and Drug Administration (FDA) also has guidance on this topic which states data collected on participants up to the time of withdrawal must remain in the study database for a study to be scientifically valid.

    c) When research involves deception or incomplete disclosure, CPHS typically requires participants to be debriefed and asked if they wish for their data to be withdrawn from final analysis. The wishes of the participants take precedence. For more information regarding this requirement, please see the policy on research involving deception.

    d) There may be other regulatory requirements that take priority as well. For example, when conducting research in the European Union (EU), or when enrolling individuals who are EU residents in research, the General Data Protections Regulations (GDPR) applies. The GDPR allows individuals the right to erasure (also known as the right to be forgotten) which requires investigators (data controllers) to erase all personal data concerning the individual.

2) Investigators are encouraged to outline in the informed consent form what may happen with the data provided by participants in situations where they may withdraw their participation or where their participation is withdrawn by investigators.

    a. Researchers may withdraw participants from research without the participant's consent when such withdrawal is permitted by the IRB-approved protocol or is necessary to protect the rights, safety, or welfare of the participant or others.

    b. Reasons for investigator-initiated withdrawal may include:

        i. Participant noncompliance with study procedures;

        ii. Safety concerns or adverse events;

iii. Discover of new exclusion criteria;

iv. Investigator judgement that continued participation is not in the participant's best interest;

v. Termination of study funding or study closure; or

vi. Other protocol-defined reasons.

c. Investigators must describe circumstances under which participants may be involuntarily withdrawn in the protocol and the informed consent document.

d. When a participant is withdrawn by the investigator:

i. The reason for withdrawal must be documented in study records;

ii. The participant should be informed of the withdrawal and any necessary follow-up procedures unless doing so would create additional risk; and

iii. Previously collected data may be retained and analyzed consistent with applicable regulations and the informed consent document.

e. The investigator-initiated withdrawals indicate unanticipated risks involving risks to subjects or others, problems with study conduct, potential noncompliance, or a pattern of participant harm, then the investigator must assess whether reporting to CPHS is required under the UAP or noncompliance policies.

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Vulnerable Populations in Research

This policy sets forth both the criteria and process when reviewing research that involves human participants from a vulnerable population. In general, the definition of vulnerable populations in research applies to individuals who lack, or believe they lack, free will or decision-making capacity, either contextually or cognitively or legally, to make informed, voluntary decisions, and are therefore potentially more susceptible to coercion, exploitation, or undue influence.

CHPS reviews research involving vulnerable populations as defined by the federal regulations (45 CFR 46.111(b); 21 CFR 56.111(b)) to ensure that the research includes additional applicable safeguards to help protect the rights and welfare of such participants.

CPHS considers the following groups as vulnerable populations:

1) Pregnant Women, Human Fetuses and Neonates
2) Prisoners
3) Children
4) Individuals with impaired decision-making capacity
5) Individuals who are economically, socially, or educationally disadvantaged
6) Individuals who, given the circumstances or context, could experience coercion or undue influence or where there is a power dynamic (e.g., researchers and their own children, instructors and their own students, supervisors and their subordinates)

When either some or all of the research participants are likely to be vulnerable to coercion or undue influence, CPHS requires one or more individuals who are knowledgeable about or experienced in working with the vulnerable populations to take part in the review of research.

CPHS recognizes that certain research activities, particularly large-scale data analyses and secondary research using public health or administrative datasets, may incidentally include information about individuals who are or were members of populations afforded additional regulatory protections (e.g., prisoners or pregnant persons). In such cases, the mere presence of these data does not require application of the corresponding regulatory subparts. Additional protections are required when the research is designed to *intentionally recruit, prospectively enroll and interact with, or specifically analyze* individuals as members of a vulnerable population, or when investigators have knowledge at the time of enrollment that subjects meet the criteria for those populations.

When CPHS reviews research enrolling vulnerable populations, CPHS applies the required additional federal regulations, as well as state and local laws, where applicable.

1) CPHS evaluates whether additional safeguards have been incorporated into the research to ensure researchers are protecting the rights and welfare of vulnerable participants.
2) The regulations at 45 CFR 46 offer additional subparts that stipulate extra protections for enrolling certain vulnerable populations in research, and that also specify requirements

for IRBs. When research involves members of one of the Health and Human Services (HHS) recognized vulnerable populations, the IRB and researchers must comply with the following regulations:

a) Subpart B—Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

b) Subpart C—Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

c) Subpart D—Additional Protections for Children Involved as Subjects in Research

i) The Food and Drug Administration (FDA) regulations also require IRBs to determine that research involving children complies with part 50, subpart D.

3) CPHS reviews and approves research enrolling vulnerable populations according to the applicable regulations and subparts; it utilizes checklists when assessing and making determinations.

CPHS recognizes that individuals and populations who may be considered vulnerable under federal regulations are entitled to both appropriate protections *and* equitable opportunities to participate in research. Protections for vulnerable subjects are intended to safeguard rights, welfare, and autonomy, and should not unnecessarily restrict participation in research or limit access to the potential benefits of research participation. CPHS will ensure that additional safeguards are proportionate to the risks of the research and tailored to the specific vulnerabilities present, rather than applied as categorical exclusions.

CPHS Review Considerations and Procedures

1) CPHS, not researchers, will determine whether regulatory requirements for additional protections apply based on the design and intent of the research.

2) When CPHS reviews research that intends to enroll vulnerable populations, reviewers carefully consider the following elements:

a) Strategies to select and recruit participants into the research; issues around informed consent and participants' willingness to volunteer; precautions against coercion, exploitation, and undue influence; and safeguards for confidentiality of data.

b) Group characteristics related to economic, social, physical, and environmental conditions, to ensure that the research builds in additional safeguards for vulnerable participants.

3) PIs are not permitted to exclude certain groups of participants from research that may be beneficial because of a perceived notion that the group has limitations or complications preventing them from enrolling in research.

a) To illustrate, PIs should not exclude potential research participants who may be developmentally delayed merely because they may require additional support throughout the consent process.

4) CPHS applies the state or local laws of the jurisdiction where the research is to take place when they review research involving vulnerable research participants. That is to say, CPHS follows state statutes regarding competency to consent for research, emancipated minors, legally authorized representatives, the age of majority for research consent, and the waiver of parental permission for research. CPHS will consult with legal counsel as needed.

5) In reviewing research involving individuals or populations who may be vulnerable to coercion or undue influence, CPHS will evaluate whether proposed protections are appropriate, proportionate, and responsive to the specific context of the research. CPHS will avoid requiring additional safeguards or exclusions that are not scientifically or ethically justified, recognizing that overly restrictive protections may unintentionally limit opportunities for participation and reduce the applicability of research findings to populations who may benefit from the research.

Research Involving Pregnant Participants, Human Fetuses and Neonates

1) Until 2018, the federal regulations defined pregnant participants as a vulnerable population. The 2018 revisions to Common Rule, however, removed pregnant participants as a vulnerable population in research. This act of revising the definition rectifies the implicit notion that women who are pregnant lack the capacity to make informed, voluntary decisions.

    a) While the 2018 revisions to Common Rule removed pregnant participants as a vulnerable population in research, there were no similar changes to Subpart B of the Common Rule which addresses Additional Projections for Pregnant Women, Human Fetuses and Neonates Involved in Research. As a result, Subpart B of 45 CFR 46 still stipulates additional safeguards for pregnant participants as well as human fetuses and neonates.

2) As stipulated in 45 CFR 46.202(f), women are considered to be pregnant if they exhibit "any pertinent signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery."

3) According to the federal regulations at Subpart B of 45 CFR 46, CPHS may approve research involving pregnant participants and fetuses if it concludes that all of the following criteria have been met:

    a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses (45 CFR 46.204(a));

    b) Research interventions, tests, or procedures are no more than minimal risk to the pregnant participants or the fetus (45 CFR 46.204(b));

    c) Any risk is the least possible for achieving the objectives of the research (45 CFR 46.204(c));

    d) Research in pregnant participants offers generalizable knowledge that cannot be acquired from nonpregnant participants ((45 CFR 46.204(d));

e) Each participant who consents to the research understands fully the associated risks and "the reasonably foreseeable impact of the research on the fetus or neonate" (45 CFR 46.204(f));

f) Inducements, monetary or otherwise, will not be offered to terminate the pregnancy (45 CFR 46.204(h));

g) Individuals engaged in research will not have any part in determining the viability of a neonate (45 CFR 46.204(j)).

4) According to the federal regulations at Subpart B of 45 CFR 46, CPHS will determine the appropriate requirements for informed consent regarding the including of pregnant women according to the following:

a) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of direct benefit to both the pregnant woman and the fetus, or no prospect of direct benefit to either the woman nor the fetus, but the risk is minimal (and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means), consent from the pregnant woman is sufficient for enrollment;

b) If the research holds out the prospect of direct benefit solely to the fetus, then both the pregnant woman and the father must provide informed consent;

i) The father's informed consent must not be obtained if he is unable to consent because of unavailability, incompetence, temporary incapacity, or the pregnancy resulted from rape or incest.

Research Involving Prisoners

1) CPHS may review research involving prisoners as participants.

a) The CPHS Administrator and staff will ensure that a majority of the CPHS will have no association with any prison involved in research conducted under the authority of CPHS (45 CFR 46.304(a))

b) CPHS will also ensure that the committee is constituted with at least one prisoner representative with appropriate background and experience to serve in that capacity and members will be identified as such on the CPHS roster (45 CFR 46.304(b))

c) CPHS will ensure that research is approved only if it finds that all the requirements under 45 CFR 46.305(a) have been met, including:

i) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

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ii) The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;

iii) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that research project;

iv) The information is presented in language which is understandable to the subject population;

v) Adequate assurance exists that parole boards will not consider a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

vi) Where CPHS finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, considering the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

2) CPHS will ensure that any review of prisoner research represents one of the following categories:

a) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects (45 CFR 46.306(a)(2)(i));

b) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects (45 CFR 46.306(a)(2)(ii));

c) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology medicine and ethics, and published notice, in the Federal Register, of his intent to approve such research (45 CFR 46.306(a)(2)(iii)); or

d) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology medicine and ethics, and published notice, in the Federal Register, of his intent to approve such research (45 CFR 46.306(a)(2)(iv)).

3) For the purposes of this policy and as per 45 CFR 46.303(c), a 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.

4) If the research involving prisoners is federally funded, CPHS will ensure that the research has certified to the DHHS Secretary that the federal requirements have been met.

Research Involving Children

1) In the research setting, children are considered a vulnerable population.

   a) Both the Common Rule (45 CFR 46) and FDA regulations include Subpart D: Additional Protections for Children as Research Subjects.

   b) Subpart D establishes risk-benefit categories for research involving children.

      i) Only research that fits into one of the first three categories in the reference table below may be approved by CPHS; the fourth category requires the approval of the Secretary of the Department of HHS.

2) California state laws allow minors 12 and older to consent for themselves to participate in research when minors access certain health services that also offer an opportunity to take part in research.

   a) When research solely involves specific treatments or procedures for which minors can give consent outside the research context (under applicable state and local laws, for example, research on sexually transmitted diseases or pregnancy), these minors would not meet the definition of children as defined at 45 CFR 46.402(a). In this instance, CPHS would not apply subpart D when reviewing the research, nor would parental permission (or waiver thereof) be considered. Under these circumstances, minors may consent for themselves to be in research.

3) CPHS chairs and designated CPHS reviewers are required to assess and categorize the risks of research into one of the allowable categories detailed in the reference table below.

4) ***Parental Permission.*** As stipulated in 45 CFR 46.408(b) and 21 CFR 50.55 (e), CPHS must determine that PIs have adequately described the provisions made to solicit and obtain permission from each child's parents or guardians.

   a) When CPHS approves research to be conducted under 45 CFR 46.404 (21 CFR 50.51) or 45 CFR 46.405 (21 CFR 50.52), it may find that the permission of one parent or guardian is sufficient.

      i) Whether CPHS determines that permission should be obtained from one or both parents will be documented with rationale in the electronic IRB system and in correspondence to the PI.

b) When CPHS approves research conducted under either 45 CFR 46.406 or 45 CFR 46.407, both parents must give their permission for their child to participate in research, unless:

   i) One parent is deceased, unknown, incompetent, or not reasonably available; or

   ii) When only one parent has legal responsibility for the care and custody of the child.

      (1) **Not reasonably available** means that a parent cannot be present during the informed consent process or is unavailable before research procedures begin. In other words, a parent is not contactable by phone, mail, email or fax, or their whereabouts are unknown.

         (a) In some cases, **not reasonably available** means that a parent should not be contacted about giving permission for research, owing to the nature of the relationship that exists between the parent and child participant (e.g., domestic violence, harmful situations to the child's health and welfare).

c) Parents or guardians must receive the elements of informed consent that have been detailed at 45 CFR 46.116(a) (1-8) and 21 CFR 50.25(a) (1-8). CPHS will determine whether additional elements are deemed necessary. Regulatory requirements (45 CFR 46.408(b)) for documenting parental permission remain the same as for informed consent.

d) CPHS may waive the requirement to obtain parental permission from parents or legal guardians, provided that the:

   i) Approved research satisfies the regulatory criteria in 45 CFR 46.116(f)(3) (1-4):

      (1) The research involves no more than minimal risk to participants.

      (2) The research could not practicably be carried out without the requested waiver or alteration.

      (3) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

      (4) The waiver or alteration will not adversely affect the rights and welfare of participants.

      (5) The research has been designed in such a manner that protects the child participants (e.g., from child neglect or child abuse), and that neither parental nor guardian permission would be a reasonable requirement.

      (6) The appropriate mechanism has been substituted to protect children as research participants, which remains aligned with federal, state, or local laws.

         (a) 45 CFR 46.408(c) provides that in addition to the provisions for waiver contained in 45 CFR 46.116(a), if the IRB determines that a research protocol is designed for conditions, or for a research population, for which parental or guardian permission is not a reasonable requirement to

protect the participants (e.g., neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(b) According to this provision, waiver of parental permission is permitted when it is not a reasonable requirement to protect subjects provided:

(i) An appropriate mechanism for protecting the children who will participate as subjects in the research is substituted (e.g., require assent of teenagers who are mature enough to fully comprehend the research activities, appointing an advocate who provides permission for the child, or appointing an assent monitor) and

(ii) The waiver is not inconsistent with federal, state, or local law (e.g., PI is requesting waiver of parental permission involving access to FERPA covered records that may not be used without parental permission or requesting a waiver of parental permission for FDA governed research involving children).

5) **Assent.** 45 CFR 46.408(e) dictates that IRBs assume the responsibility for determining how assent from children must be obtained and documented.

a) If the research involves children and the investigator has not requested or CPHS has not granted a waiver of alteration of informed consent, permission from a parent (either one or two) and assent of children aged 7 or older must be obtained.

i) For children 7-12 years old, a simplified assent form and a verbal “yes” from the child may be sufficient dependent on the study.

ii) For children 13-17, a comprehensive assent form is required as adolescents should be fully informed about the study and agree to their own participation in research by signing the document.

b) **Assent Waiver**. CPHS may waive the requirement to obtain assent if either:

i) some or all child participants are incapable of assenting; or

ii) the research has the prospect for direct benefit to the participant; or

iii) the research qualifies for informed consent to be waived, outlined above in 4)d)i.

6) Children who have turned 18 years of age while participating in research are considered adults; for this reason, they must consent to remain enrolled in research. CPHS will determine and document with sufficient detail when re-consenting minors is required.

a) If the research procedures are limited to data analysis, re-consent is not required.

b) If any research procedures remain for which CPHS has required informed consent, the 18-year-olds must consent to continue their participation in the research. The procedures requiring consent could include but would not be limited to:

   i) study visits;

   ii) continuation of study intervention;

   iii) collection of data that is identifiable; and/or

   iv) use of individually identifiable specimens or data under future use provisions of the informed consent form

7) **Wards**. Children who are wards of the state, or any other agency, institution, or entity, can be enrolled in research involving greater than minimal risk without the prospect of direct benefit to individual participants, but likely to yield generalizable knowledge about the participant's disorder or condition (45 CFR 46.406; 21 CFR 50.53) on the condition that the research is:

   a) Related to their status as wards; or

   b) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved are not wards.

   If the research proposal fulfils the condition(s) outlined above:

   i) An advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in *loco parentis.*

   ii) Advocates must possess the background and experience to act in the best interests of the child while the child participates in the research for its entire duration.

   iii) Advocates must not be associated with the research whatsoever (e.g., with CPHS, researchers, or the guardian organization) except while serving as an advocate.

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Participants with Impaired Decision-Making Capacity

1) Research warrants special attention when it proposes to enroll participants who have impaired decision-making capacity. Research involving this vulnerable population could present risks that might be greater than minimal; the research might not offer the participants any direct benefits. Importantly, the research design could place these vulnerable individuals at greater risk of being coerced or unduly influenced to participate.

2) CPHS reviews and approves research that involves enrolling participants with impaired decision-making capacity by considering the following:

    a) context in which the research takes place,

    b) complexity and rigor of the research procedures, and

    c) monetary compensation, if any, offered.

3) When research involves individuals with diminished decision-making capacity, CPHS will review both the research design and the consent process, evaluating whether the proposed research:

    a) Has an adequate plan to assess participants' capacity to consent.

        i) CPHS could require PIs to assess participants' competency whenever a possibility exists of enrolling participants with impaired decision-making capacity.

        ii) CPHS strongly recommends PIs employ assessment methods that directly evaluate participants' ability to comprehend the proposed study, judge the risks and benefits of the research, and then decide whether to enroll.

            (1) PIs without appropriate training to make an assessment of a participant's competency may utilize clinicians to make this call but should refrain from making any judgements.

            (2) For more than minimal risk studies, non-clinician PIs may not make any assessments of competency.

        iii) Even if individuals can provide informed consent, they may refuse to participate in research, despite what their legally authorized representatives (LARs) (known as Surrogate Decision Maker in California) desire or approve. PIs should not, under any circumstances, coerce or force these individuals to participate.

    b) Does not present any significant risks, either tangible or intangible.

    a) Presents some probability of harm or injury and, if so, ensuring that there is greater probability of direct benefit to the participants.

    b) Has devised procedures ensuring that the participants' representatives are well-informed about their obligations and roles for protecting and advocating for participants with impaired decision-making capacity.

4) Decisional impairment consists of participants who:

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a) Are incompetent to provide legally effective informed consent to participate in research.

b) Are cognitively impaired.

c) Have compromised ability to make decisions in their best interests due to:

i) being under the influence of or dependent on drugs or alcohol,

ii) suffering from degenerative diseases affecting the brains, and

iii) severely disabling physical handicaps.

5) To give informed consent, the participant must be given all relevant information pertinent to the decision and be able to recognize that a decision is needed, and process the information (e.g., discuss it, remember it, evaluate the various factors, and understand the consequences). This process may be compromised due to external factors such as time limitations or stress.

6) CPHS recognizes that research involving participants who are either decisionally impaired or legally incompetent could vary according to circumstances, situations, or degrees of impairment or incompetence.

a) Research participants could be considered mentally or cognitively impaired but still be able and have the capacity either to provide informed consent or to refuse to participate in research. In other cases, mentally or cognitively impaired participants cannot provide informed consent because they lack decisional capacity and, in such cases, researchers would obtain consent from a LAR.

7) CPHS will determine when assent from a mentally or cognitively impaired subject is required if consent is provided by a LAR, when appropriate.

8) CPHS will ensure that at least one member who is an expert in decisional impairment, or who works with individuals with limited decision-making capacity, will be present during the review of research. If CPHS does not have this expertise in their membership, they can consult with an individual with similar background.

a) CPHS may consider, depending on the nature of the research, inviting an individual from the target population, a prospective participant's family member(s), or a representative of an advocacy group for that population.

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Individuals who are Economically, Socially or Educationally Disadvantaged

1) CPHS reviews research involving economically, socially, or educationally disadvantaged populations to ensure that additional protections are included in the study design to minimize risks to the participants.

    a) Populations that may be considered economically or educationally disadvantaged include, but are not limited to, individuals who live in poverty, who are homeless, who have a low income or limited access to health care, and those who have limited educational attainment.

    b) Populations that may be considered socially vulnerable can derive from group experiences and typically involve some damage or harms to the community (e.g., indigenous communities, LGBTQ+).

2) Individuals who are receiving services or assistance from a public entity should be assured during the consent process that participation, or choosing to not participate, in the research will not affect their eligibility for the state services, unless this is identified appropriately in the informed consent document.

3) Special consideration will be given to the informed consent form and process to ensure that individuals have the capacity to understand the information being provided and the voluntary nature of their participation.

4) Consideration will be given to both the amount and method of reimbursement to individuals who are economically, socially, and educationally disadvantaged to ensure against undue influence.

5) Investigators must ensure submissions include sufficient detail regarding how risks will be mitigated to secure CPHS approval for research involving these vulnerable populations.

Individuals who, given the circumstances or context, could experience coercion or undue influence or where there is a power dynamic

Students

1) CPHS is supportive of research involving students when the risks to participants are minimized, when investigators take special precautions to ensure the rights and welfare of participants are protected, and when students are not compelled to participate in research.

2) The federal regulations require investigators to obtain consent for participation in research when the possibility of coercion or undue influence is minimized. When investigators recruit students to participate in research, special consideration should be given to ensure that any possibility of coercion or undue influence is minimized.

3) Non-physical risks are considered when an investigator plans to recruit students. Non-physical risks include but are not limited to:

    a) Stigma or reputational harm that could result from a breach in confidentiality or accidental disclosure of confidential information

    b) Impact on the student's educational experience

Federal Requirements for Students

Federal regulations such as the Family Educational Rights and Privacy Act (FERPA) and the Protection of Pupil Rights Amendment (PPRA) apply to research involving students, in addition to the Common Rule regulations.

FERPA requires that schools obtain written consent from parents or students (if the student has reached the age of 18 or is attending an institution of post-secondary education) prior to the release of personally identifiable information from an education record that goes beyond basic directory level information, such as name, telephone number, or dates of attendance.

PPRA requires that written consent be obtained from students (if they are an adult or emancipated minor) or parents of minors before students can participate in surveys, analysis, or evaluation that involves one or more of the following eight topics:

a) political affiliations or beliefs of the student or the student's parents'

b) mental and psychological problems of the student or the student's family;

c) sex behavior or attitudes;

d) illegal, anti-social, self-incriminating or demeaning behavior;

e) critical appraisals of other individuals with whom respondents have close family relationships;

f) legally recognized privileged or analogous relationships, such as those with lawyers, physicians, and ministers;

g) religious practices, affiliations, or beliefs of the student or student's parents; and/or

h) income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program)

Employees

CPHS is supportive of research involving employees when the risks to participants are minimized and when investigators take special precautions to ensure the rights and welfare of participants are protected.

The federal regulations require investigators to obtain consent for participation in research when the possibility of coercion or undue influence is minimized. When investigators recruit California HHS employees to participate in research, special consideration should be given to ensure that any possibility of coercion or undue influence is minimized.

If possible, investigators should design research in a way that blinds them to the identity of the employees who participate in research. Employees who decline to participate in research should not be penalized through performance evaluations or consideration of job advancement. Alternatively, participation of employees in research should not bestow any type of occupational advantage over staff who decline participation.

The informed consent form should clearly state that the decision not to participate or to withdraw participation will not have any negative consequences for the individual being recruited such as consideration of bonus, promotion, and work evaluations.

Recruiting Research Subjects

Recruitment methods and advertisements that will be used in human subjects research require prospective review and approval by CPHS. Federal guidance and CPHS considers advertising or soliciting study participants to be the start of the informed consent process. PIs must provide detailed information regarding how participants will be identified, contacted, and recruited in the CPHS application. CPHS evaluates this information to ensure recruitment is fair and equitable and that advertisements do not unduly influence potential subjects or overestimate possible benefits of participation.

When CPHS review authority exists solely because CalHHS personnel or state-held identifiable information are used to facilitate participant recruitment, screening, or informed consent activities, review under this policy is limited to those activities and does not constitute review or approval of the complete research protocol.

In addition, CPHS will ensure that regardless of how initial contact occurs, the methodology used must respect the potential participant's privacy and confidentiality of their information. Lastly, CPHS will ensure that the process of identification and recruitment of research participants complies with applicable federal and state laws for privacy and confidentiality. See the Privacy Policy for additional information on CPHS' requirements to use and/or disclose PHI for research recruitment purposes.

Any contact with a potential research participant must be conducted by a research team member who has the appropriate training is part of the approved research team as described in the CPHS application.

Advertisements

Advertising is a common method used by researchers to solicit potential subjects for participation in research. Examples of advertisements include flyers, brochures, television ads, radio ads, social media ads, etc. Investigators must obtain CPHS approval prior to the use of all television, radio, print advertisements, e-mail solicitations, letters, websites, and other recruitment methods and materials intended for the recruitment of prospective research participants. Advertisements must be submitted to CPHS in their final form to receive approval for use.

Advertisements used to recruit research subjects should be limited to the information that a potential subject would need to determine if they are eligible and interested in participation. All advertisements must be approved by CPHS prior to posting. Advertisements may include but are not limited to the following information:

1) The name of the PI and contact information for participation/questions.
2) The purpose of the research.
3) The criteria that will be used to determine eligibility for the study.
4) A brief list of benefits to participation, if any (note that compensation for participation is **not** considered a benefit).
5) The payment of any compensation and potential reimbursement for research related expenses (e.g., travel, meals, etc.). See below for additional details.
6) The time or other commitment required of the participants.
7) The words “Research” or “Research Study.”
8) The CPHS study number (if the study is reviewed and approved by another IRB, inclusion of that IRB’s study number is acceptable).

What is not acceptable in advertisements?

CPHS does not allow recruitment methods or advertisements which are misleading, inaccurate, exculpatory, coercive, or unduly influential. CPHS will review advertisements to ensure that they **do not:**

1) State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the informed consent form and protocol.
2) State or imply a certainty of receipt of a study drug, device, or intervention in lieu of receiving the study placebo (if applicable).
3) Include exculpatory language (i.e., any language that attempts to waive a participant's legal rights or releases investigators, sponsors, or institutions from liability for negligence or malpractice).
4) Emphasize the payment or compensation for participation in the research, by such means as larger or bold type. (Note**:** The dollar amount to be paid to participants may be included in advertisements. However, CPHS may determine that stating the specific amount is coercive or unduly influential. In these instances, CPHS will only allow the advertisement to state that compensation will be offered without including the dollar amount.)
5) Promise “free treatment” or treatment at “no cost” when the intent is only to say participants will not be charged for taking part in the research.

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Additional considerations for advertisements for FDA-regulated research

CPHS advises all investigators conducting research subject to FDA regulation to review the FDA Information Sheet ***Recruiting Study Subjects***. The IRB will review advertisements for FDA-regulated research to ensure that the advertisements **do not:**

1) Make claims, either explicitly or implicitly, about the drug, biologic or device under investigation that are inconsistent with FDA labeling (e.g. stating the test article is known to be equivalent or superior to any other drug, biologic or device; that the test article is safe for the research use; or that the test article is approved for the research use).
2) Use terms such as “new treatment”, “new medication” or “new drug” without explaining that the test article is investigational.
3) Allow compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Compensation to Research Subjects

CPHS reviews the amount and method of compensation to research subjects and the proposed payment schedule to ensure the compensation does not present undue influence (an offer of an excessive or inappropriate reward or other overture in order to obtain compliance) to individuals participating in CPHS approved research. CPHS will consider whether compensation to participants is just and fair. CPHS must also consider the study population and the context of the research to judge how compensation might affect participants.

Compensation should be based on the time an individual will be involved with study procedures, the inconvenience or discomfort to the subject, and reimbursement for expenses incurred while participating. Studies involving multiple interactions over time should offer prorated compensation as opposed to upon completion of the study. Compensation that includes a bonus for the completion of the study is allowable if it is reasonable and not so large that it would unduly influence individuals to continue participation when they would have otherwise withdrawn from the research study.

PIs should describe in the CPHS application and the informed consent document the amount, method, and terms of payment of any compensation to research participants. The description should include the conditions under which the participant would receive partial or no payment and what will happen if the participant withdraws prior to study completion. Any changes to the amount, method or terms of payment must be approved by CPHS prior to changes being implemented.

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Compensation is not viewed as a benefit to participation in research and should not be outlined as such in the informed consent document or considered by CPHS in the assessment of the risks and benefits to subjects.

The federal regulations require additional protections for certain populations who may be vulnerable to coercion or undue influence. Inducements that would ordinarily be acceptable in some populations may become undue influences for these populations and therefore, compensation to these populations will receive additional ethical scrutiny.

1) CPHS will consider equity across demographics when reviewing compensation among the study population (e.g., if enrolling both children and adults, the expectation is that compensation will be equivalent if study procedures are the same)

2) When considering the amount of compensation to be given to a child and/or the child's parents, the amount of compensation should not be so large that parents would put undue pressure on the child to assent to participate. Special consideration must be given to ensure that the child does not simply assent to participate based on the amount or type of compensation. In addition, PIs should make every effort to establish a reimbursement amount and schedule that will not be a factor in the child's decision to participate or the parent's decision to give permission for the child's participation.

3) Compensation to research subjects participating in international research will be reviewed by CPHS to ensure the amount is appropriate and reflective of the standard of living in the country in which the research is being conducted and the subject's income.

Transnational Research

As per CalHHS policy, CPHS cannot approve research where personally identifiable data held by CalHHS are being transferred outside the United States.

The following information is relevant only to research where CPHS is serving as the IRB of record for regulated research a prospective study conducted outside the US.

CPHS reviews research that is conducted internationally (or transnationally) to ensure it is consistent with the ethical principles established in the Belmont Report. In addition, researchers are expected to comply with the US regulations and guidelines and any applicable regulations of the country in which the research is conducted. OHRP provides guidelines that govern human subjects research in foreign countries, as well as standards from a number of international and regional organizations. More information on OHRP's International Compilation of Human Research Standards can be found here.

Researchers should:

1) Strive to meet the same or equivalent levels of protection for participants internationally just as they would if the research was exclusively conducted in the United States.

2) Comply with local laws and take the cultural context of the country in which the research will be conducted into account when preparing the application for CPHS review.

3) Implement an informed consent process that is consistent with the cultural norms of the country in which the research is being conducted and translate the informed consent form into a language that is understandable by the subject.

4) Ensure post-approval monitoring for research involving greater than minimal risk.

5) Obtain approval from an ethics committee (or similar committee) should one exist in the host country and provide documentation of the approval to CPHS.

CPHS will ensure the review of international research will involve members who possess knowledge of the local research context for the country in which the research will take place. Should existing committee members not possess this expertise, Consultants may be used to facilitate the review of international research.

Investigator Responsibilities

Principle Investigators who submit research to CPHS for review and approval are responsible for directing and overseeing all aspects of the proposed research activities and must ensure the following (this is not an exhaustive list):

1) Research is conducted in an objective and unbiased manner in compliance with applicable regulations, state law, and CPHS policies.

2) The protection of the safety, rights, and welfare of human research participants is paramount.

3) Submission to, and approval by, CPHS is secured prior to the initiation of research activities.

4) Continuing review and approval is secured or annual check-in of research is acknowledged, as applicable, in a timely manner and prior to the expiration of the study.

5) Submission of a closure form is submitted to CPHS and acknowledged upon the completion of the research study.

6) The conduct of research is in compliance with the approved protocol, relevant regulations, laws, and CPHS policies.

7) CPHS approval is secured prior to the initiation of modifications to a study, except for those changes that are implemented to eliminate immediate hazards to participants.

8) A timely response to all inquires related to compliance issues with approved research.

9) Participation in post-approval monitoring, if requested by CPHS.

10) Research staff are qualified by training and experience for their research roles, including knowledge of applicable regulations, laws, codes and guidance, professional standards, and CPHS policies for the protection of human subjects.

11) Subjects are recruited in a fair and equitable manner where individuals are not discriminated against based on age, race, gender, or ethnicity.

12) The informed consent process and method of documentation are appropriate for the type of research being conducted and the study population.

13) The availability of medical or psychosocial resources for participants, as applicable for the study.

14) Processes are in place to address research subject complaints, concerns, or requests for information.

15) Prompt suspension or termination of research, as appropriate, when the rights, safety, or welfare of subjects are violated and submit reports of these actions and other reportable events to CPHS within two (2) business days of taking such action.

16) Disclosure of financial conflicts of interest that may be related to the research under review by CPHS.

17) Responsibility for project activities has been delegated appropriately to others (i.e., research team members) and in writing. Note, however, that the PI is ultimately responsible for compliance with all applicable regulations, state laws, and policies and for ensuring a safe research environment for participants.

18) Participants are notified of any changes or new information that may affect their willingness to continue their participation in the research.

19) Prompt reporting to CPHS of any unanticipated problems, concerns or complaints by research subjects, and serious or continuing noncompliance with applicable regulatory requirements or determinations.

20) All research records are maintained in compliance with applicable regulations, state law, and CPHS policies.

21) CPHS is notified immediately of any audit/inspection by the FDA and any sanctions or actions taken against the investigator, Sponsor, or the research. This includes research which has been reviewed and approved by another IRB and CPHS has reviewed the project under the IPA.

22) Keep the RO appraised of significant changes in the design or conduct of the research.

23) Submit an amendment to CPHS if there is a change in the RO.

Responsible Official Responsibilities

CPHS requires applications to include the name of an individual who can serve as a Responsible Official (RO) for the research project. The RO must be someone from the same institution as the PI and must hold an ongoing supervisory or administrative position over the PI.

Responsibilities of the RO include:

1) Authority to ensure compliance with all institutional policies, regulations, state law, and CPHS policies for research involving human subjects, including data security requirements.

2) Maintaining Institutional oversight and accountability for how the data is managed, protected, and used throughout the project.

3) Serving as the Institution's representative for the project and primary point of contact if the PI becomes unavailable for any reason and is unable to respond to CPHS inquiries.

4) Ensures oversight of the research if the PI were to leave the institution for any reason and a new PI has not been approved by CPHS.

5) Speaking on behalf of the institution, coordinating any required actions, and addressing concerns related to compliance, data security, or project oversight.

6) Serving as the point of escalation in situations where there are concerns about the PI's availability or responsiveness.

7) Ensuring the institution fulfills all obligations associated with the project.

For projects where a student serves as the PI, the RO should be the faculty advisor or supervising faculty member. For other types of projects, the RO is typically a department chair, division director, unit chief, or a vice president who directly oversees the PI's research.

Institutional Data Security Requirements

When reviewing projects under the IPA only, CPHS can only approve applications if the transfer of the data is within the Continental U.S.. The Institution is responsible for the primary storage, receipt, and management of study data, and for maintaining data security and regulatory compliance. In the event of an adverse incident or breach of confidentiality, accountability rests with the PI and RO.

The main site(s) refers to the institution(s) responsible for the primary storage, receipt, and management of study data, as well as for ensuring data security and compliance with relevant regulations. This includes overseeing access controls, data encryption, and privacy safeguards. Typically, this is PI and RO's institution, which houses and manages the servers through which the data are processed. If an unanticipated problem occurs, including a breach in confidentiality, the PI and RO are responsible for timely reporting.

For each site participating in the research and storing data, a Co-Investigator must be named in the CPHS application, and the Institution must sign a Data Security Letter acknowledging compliance with CalHHS data security policies and the Data Use Agreement.

FDA Regulated Research

The U.S. Food and Drug Administration (FDA) regulates the marketing of new drugs, biologics and devices. FDA's regulations specify the circumstances under which either an Investigational New Drug (IND) application (21 CFR 312, 361) or an Investigational Device Exemption (IDE) application (21 CFR 812) are required prior to conducting a clinical investigation.

When a marketed drug or device is the subject of proposed research, investigators are required to submit their determination that the research meets the requirements for exemption from these requirements if an IND or IDE number is not provided in the application materials to CPHS. PIs must also submit supporting documentation to allow CPHS to concur or disagree with their determination that an IND or IDE is not required for that use. If uncertainty exists, the IRB may resolve the matter by requesting that the investigator consult with FDA.

The following sections apply to CPHS review of research involving drugs and devices in clinical investigations.

Research Involving Drugs

This policy sets forth both the criteria and process to review research that involves drugs or biologics (referred to in this policy as "drugs") to protect the rights and welfare of human subjects involved in such research (or clinical investigations) as directed by the Department of Health and Human Services (DHHS) and by the Food and Drug Administration (FDA).

CPHS applies FDA regulations to research studies involving drugs when the activity meets the definition of a clinical investigation involving a test article under 21 CFR 56.102, regardless of funding.

CPHS is responsible for evaluating whether the study involves:

1) A drug as defined by the FDA; and
2) Administration or dispensing of the drug in an experiment to one or more human subjects, except when a marketed drug (i.e., FDA approved) is used in the course of medical practice.

If both of the above items are confirmed by CPHS, this is considered a clinical investigation and an Investigational New Drug application (IND) is required for the study unless the study meets criteria for an IND exemption under 21 CFR 312.2(b).

An IND may go into effect:

1) 30 days after FDA receives the application, unless FDA notifies the sponsor that the investigations described in the application are subject to a Clinical Hold; or
2) on earlier notification by FDA that the clinical investigations in the IND may begin.

CPHS reserves the right to require investigators to obtain documentation from the FDA that the proposed use of a drug in a clinical investigation qualifies as exempt from the prior submission requirements (i.e., IND Exempt).

CPHS utilizes a checklist review method to ensure that human participants will be protected while participating in research with drugs. The checklist contains the FDA requirements to ensure that the drug is appropriately classified.

Definitions

1) **Clinical Investigation:** Any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. (21 CFR 56.102(c))

2) **Human Subject (FDA only):** an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. (21 CFR 56.102(e))

3) **Sponsor:** a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. (21 CFR 56.102(j))

4) **Sponsor-Investigator:** an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. (21 CFR 56.102(k))

5) **Test article:** any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act. (21 CFR 56.102(l))

Off-Label Use of an FDA-Approved Drug

“Off-Label use” means the use of legally marketed and/or FDA-approved drug for a purpose or in a manner not already approved by the FDA. Off-label use of a marketed product by a physician, when the intent is the “practice of medicine” (i.e., diagnosis, cure, mitigation, treatment, or prevention of disease in humans), does not require the submission of an IND or review by CPHS.

If the off-label use of an FDA-approved product is intended to collect data about the product’s safety or efficacy, or for other non-diagnostic or non-therapeutic purposes, or if the use significantly increases risk to participants, an IND is generally required if human research participants are involved. Physicians should consult with the FDA Center for Drug Evaluation and Research to determine when data collection for off-label use may require an IND.

Expanded Access

The FDA allows certain individuals not enrolled in clinical trials to obtain expanded access to investigational drugs, agents, or biologics under the certain circumstances. Prior to submitting

an application to CPHS for approval of an expanded access protocol, PIs are encouraged to review the FDA guidance on same.

Circumstances in which the FDA allows for expanded access to drugs, agents and biologics:

- Patients who have ***a serious or immediately life-threatening disease or condition,*** and there is no comparable or satisfactory alternative therapy to diagnose, monitor or treat the disease or condition;
- Potential ***patient benefit justifies the potential risks of the treatment*** and the potential risks are not unreasonable in the context of the disease or condition to be treated; and
- Providing the investigational drug for the requested *use* ***will not interfere with clinical investigations that could support marketing approval*** of the expanded access use or otherwise compromise the potential development of the expanded access use.

There are three different types of expanded access programs:

1) **Individual patient** – typically limited to a single course of treatment for a single patient when the patient cannot obtain the drug under another IND or protocol (i.e., there is no other clinical trial available for which the patient can enroll).

2) **Intermediate size patient populations**– use by more than one patient, but generally fewer patients than in a treatment IND or protocol.

3) **Treatment IND/Protocol** - This type of expanded use of an investigational drug outside of a controlled clinical trial is intended for *widespread treatment use*. The FDA must determine that: (a) the drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use or that all clinical trials of the drug have been completed; (b) the sponsor is actively pursuing marketing approval of the drug; and (c) there is sufficient clinical evidence of safety and effectiveness to support the expanded access use.

PIs are encouraged to specifically state in their application to CPHS that they are seeking approval for an expanded access protocol. This type of research is typically categorized as greater than minimal risk and thus, requires review and approval by the convened committee. Expanded access protocols will undergo the same process for review as described above in the Initial Review section of this manual. If you have any questions regarding expanded access protocols, please contact the CPHS Office.

Procedures for Review of Research Involving Drugs

1) Investigators must complete and submit an initial submission packet (or modification if adding or changing the use of a drug throughout the conduct of the study) in the IRB electronic submission system. When submitting research involving drugs, investigators should specify:

a) The drug(s) to be administered or dispensed as part of the protocol;

b) Dosing and route of administration of the drug;

c) Whether drug is currently approved by the FDA for the proposed indication or any other indication;

d) The regulatory status proposed (e.g., IND not required – approved drug and use; IND Exempt, or IND required);

e) Proposed new risks and benefits of an unapproved drug or unapproved use of an approved drug; and

f) Documentation from the FDA, if applicable.

2) CPHS evaluates:

a) Whether the use of the drug is considered research and involves human subjects (DHHS); and

b) Whether a drug administered or dispensed as part of a protocol is considered an investigational drug (or test article) and involves human subjects (FDA – 21 CFR 56.102)

3) If the activity is considered research (DHHS) not constituting a clinical investigation (FDA), then it is reviewed following requirements contained within CPHS Policy on Initial Reviews and the rest of this policy on research involving drugs does not apply.

4) If the activity is considered a clinical investigation (FDA) involving an investigational drug, CPHS will evaluate whether:

a) The proposed drug(s) are FDA-approved for any indication. If any drug proposed to be administered or dispensed is not FDA-approved for any indication, then an IND will be required to conduct the study.

i) If an IND is required, CPHS staff will confirm during the pre-review that a valid IND has been received as evidenced by:

(1) A document from the Sponsor indicating the IND number (i.e., protocol);

(2) A letter from the FDA indicating the IND number; or

(3) Other CPHS approved methods of validation.

ii) If an IND is required but the investigator has not received the IND by the time CPHS reviews the study, CPHS may contingently approve the study under the condition that valid proof of receipt of the IND has been obtained and submitted for CPHS review prior to starting the study.

b) If the proposed drug(s) are all FDA-approved for an indication, CPHS will confirm whether the uses of the drug(s) are in line with these indications. If they are all within the approved indications (including disease, route of administration, dosage, population, and all other factors), then an IND will not be required and CPHS will apply 21 CFR 50 and 56 regulations to the study only.

c) If any drug is not used in line with the approved indication on the study, CPHS will confirm whether the study meets any of the IND Exemption Criteria outlined in 21 CFR 312.2(b).

a) Per FDA guidance, the Sponsor or Sponsor-Investigator is responsible for determining whether the investigation meets the criteria for an IND exemption. (Guidance for Clinical Investigators, Sponsors, and IRBS: Investigational New Drugs Applications (INDs) - Determining whether Human Research Studies Can be Conducted Without an IND)

b) CPHS staff will pre-screen applications and assess whether the exemption justification is appropriate by reviewing the submitted information. This assessment will be included in the packet as a referral to the convened IRB for review.

c) If CPHS does not agree with the exemption justification, it will communicate this decision to the investigator and CPHS approval will not be granted until an IND number is submitted or the FDA determines that an IND is not required for the study.

d) If CPHS does agree with the exemption justification, this decision will be documented in the CPHS files and meeting minutes.

Research Involving Devices

This policy sets forth both the criteria and process to review research that involves testing the safety and effectiveness of devices to protect the rights and welfare of human subjects involved in such research (or clinical investigations) as directed by the HHS and by the FDA.

CPHS applies FDA regulations when a study involves devices used to evaluate safety or effectiveness under 21 CFR 812. If a study involves using a device but does not test the safety or effectiveness of the device, it is not impacted by this policy. It is the policy of CPHS that research involving a device, other than the use of a marketed device in the course of medical practice, must have an IDE number provided by the FDA, unless the device meets the requirements for an abbreviated IDE or the FDA IDE Exemption criteria described below.

When research is conducted to determine the safety or effectiveness of a device, CPHS must determine:

1) Whether the study is a clinical investigation of a device; and
2) Whether the use of the device is IDE Exempt; or
3) Whether the device meets the criteria for a Significant Risk (SR) or Non-Significant Risk (NSR) device.

If a device is determined to be a significant risk, an Investigational Device Exemption (IDE) issued by the FDA is required.

An IDE may go into effect:

3) 30 days after FDA receives an application, unless FDA notifies the sponsor that the investigations described in the application are subject to a Clinical Hold; or

4) on earlier notification by FDA that the clinical investigations for the IDE may begin.

If the device is determined to be a non-significant risk, the study may be eligible for the requirements of an abbreviated IDE and submission to the FDA may not be required. However, the Sponsor or Sponsor-Investigator must comply with the applicable requirements for abbreviated IDE studies under 21 CFR 812.2(b)(1).

If a PI/Sponsor believes the use of the device would be exempt from the IDE requirements, CPHS reserves the right to require investigators to obtain documentation from the FDA that the proposed use of the device in a clinical investigation qualifies as exempt from the submission requirements (i.e., IDE Exempt). Such documentation from the FDA must be included in the application to CPHS for review.

CPHS utilizes a checklist review method to ensure that human participants will be protected while participating in research with device. The checklist contains the FDA requirements to ensure that the device is appropriately classified.

Definitions

1) **Investigational Device:** a device, including a transitional device, that is the object of an investigation. (21 CFR 812.3(g))

2) **Investigation:** a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. (21 CFR 812.3(h))

3) **Investigator:** an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. (21 CFR 812.3(i))

4) **Noninvasive:** when applied to a diagnostic device or procedure, means one that does not by design or intention:

    a) Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or

    b) enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. For purposes of this policy, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive. (21 CFR 812.3(k))

5) **Significant Risk Device:** an investigational device that:

    a) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

b) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

c) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

d) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (21 CFR 812.3(m))

6) **Sponsor:** a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. (21 CFR 812.3(n))

7) **Sponsor-Investigator:** an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under FDA regulations include those of an investigator and those of a sponsor. (21 CFR 812.3(o))

8) **Subject:** a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease. (21 CFR 812.3(p))

Off-Label Use of an FDA-Approved Device

"Off-Label use" means the use of legally marketed and/or FDA-approved device for a purpose or in a manner not already approved by the FDA. Off-label use of a marketed product by a physician, when the intent is the "practice of medicine" (i.e., diagnosis, cure, mitigation, treatment, or prevention of disease in humans), does not require the submission of an IDE or review by CPHS.

If the off-label use of an FDA-approved product is intended to collect data about the product's safety or efficacy, or for other non-diagnostic or non-therapeutic purposes, or if the use significantly increases risk to participants, an IDE is generally required if human research participants are involved. Physicians should consult with the FDA to determine when data collection for off-label use may require an IDE.

Expanded Access for Medical Devices – Compassionate Use

Expanded access is a potential pathway for patients with a serious or life-threatening disease or condition to access an investigational medical device that has not been approved or cleared by the FDA for treatment outside of clinical trials and when no comparable or satisfactory alternative therapy options are available.

There are three categories:

1) **Emergency Use** - The use of an investigational device when an individual patient is in a life-threatening situation and needs immediate treatment; there are no alternative options and no time to use existing procedures to get FDA approval for the use.

2) **Compassionate Use** (for Individual Patient/Small Group Access)

3) **Treatment Investigational Device Exemption (IDE)** - The use of an investigational device to treat or diagnose a group of patients with a serious or immediately life-threatening disease or condition when the device is also being studied for the same use under an approved IDE. Treatment IDEs will be referred for review and approval by the convened board.

CPHS requires investigators wanting to access an investigational device that has not received FDA approval or clearance be a medical physician. In addition, CPHS must determine the following for approval of the unapproved device:

1) the patient has a life-threatening or serious condition;

2) there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition exists; and

3) the potential patient benefit justifies the potential risks of the investigational device.

Unlike emergency use of an unapproved device, prior FDA approval is needed before compassionate use occurs.

To review an unapproved device for expanded access/compassionate use, PIs must submit the following to CPHS using the electronic system:

1) A description of the patient's condition and the circumstances necessitating treatment

2) A discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition

3) An identification of any deviations in the approved clinical protocol that may be needed to treat the patient

4) A description of the patient protection measures that will be followed

    a) A consent form that contains the information required under 21 CFR 50.25 must be submitted for review and approval

5) Documentation of an independent assessment by a physician who is not participating in the study or in the care of the patient that concurs with the planned usage

6) Authorization from the device manufacturer on the use of the device

7) An appropriate schedule for monitoring the patient to detect any possible problems arising from the use of the device, taking into consideration the investigational nature of the device and the specific needs of the patient

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8) Evidence of FDA approval of compassionate use

9) If there is an IDE for the device, confirmation of the IDE by the sponsor

    a) If there is no IDE for the device, PIs must submit a description of the device provided by the manufacturer

Following CPHS approval and the compassionate use of the device, PIs must submit a follow up report to the FDA within 45 days. The report should include summary information regarding the patient's outcome. If any problems occurred as a result of using the device, this information should be included in the follow up documentation to the FDA. This documentation should also be submitted to CPHS for review.

Procedures for Review of Research Involving Device

1) Investigators must complete and submit an initial submission packet (or modification if adding or changing the use of a device throughout the conduct of the study) in the IRB electronic submission system. When submitting research involving devices, investigators should specify:

    a) The device to be used;

    b) Modality and intended effect of the device;

    c) Whether device is currently approved by the FDA for the indication proposed or any other indication;

    d) The regulatory status proposed (e.g., IDE not required – approved device and use; IDE Exempt; IDE required – NSR; or IDE required - SR);

    e) Proposed new risks and benefits of an unapproved device or unapproved use of an approved device; and

    f) Documentation from the FDA, if applicable.

2) CPHS evaluates:

    a) Whether the use of the device is considered research and involves human subjects (DHHS); and

    b) Whether a device used is considered an investigational device (or test article) and involves human subjects (FDA – 21 CFR 56.102)

3) If the activity is considered research not constituting a clinical investigation (FDA), then it is reviewed following requirements contained within CPHS Policy on Initial Reviews and the rest of this policy on research with devices does not apply.

4) If the activity is considered a clinical investigation (FDA) involving an investigational device, CPHS will evaluate whether:

    a) If the use of the device in the study is IDE Exempt (21 CFR 812.2.(c)). If it is considered IDE Exempt, this determination will be documented in the IRB review and no further action is required.

b) If the device is not eligible for an IDE Exemption, CPHS will determine whether the use of the device is SR or NSR.

i) Per FDA guidance, the Sponsor or Sponsor-Investigator is responsible for making the initial risk determination and presenting it to the IRB. (Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors – Significant Risk and Nonsignificant Risk Medical Device Studies)

ii) CPHS staff will pre-screen applications and assess whether the risk determination is appropriate by reviewing the submitted information. This assessment will be included in the packet as a referral to the convened IRB for review.

iii) If CPHS determines that the device is SR, then an IDE is required.

(1) CPHS will confirm that a valid IDE has been received as evidenced by:

(a) A document from the Sponsor indicating the IDE number (i.e., protocol);

(b) A letter from the FDA indicating the IDE number; or

(c) Other CPHS approved methods of validation.

(d) If prior submission to the FDA is required (i.e., IDE is required) but the investigator has not received the IDE by the time CPHS reviews the study, CPHS may contingently approve the study under the condition that valid proof of receipt of the IDE has been obtained and submitted for CPHS review prior to starting the study.

iv) If CPHS determines that the device is NSR, then submission to the FDA for an IDE is not required and the use of the device meets the criteria for an abbreviated IDE

(1) As noted in CPHS policy on Initial Reviews, all determinations for a nonsignificant risk device must be made by the convened IRB.
(2) If the Sponsor makes a determination that a device is nonsignificant risk and CPHS agrees with this determination, this confirms that the study will be conducted according the abbreviated IDE requirements (as noted above). This determination from CPHS will be documented in the IRB minutes from a convened meeting.
(3) If the Sponsor makes a determination that a device is nonsignificant risk and CPHS disagrees with this determination, both the investigator and the Sponsor will be informed of this decision. This determination from CPHS will be documented in the IRB meeting minutes.
(4) For such determinations, CPHS will document their determination that the research involves a significant risk device and will require that an IDE application be submitted to the FDA before CPHS will re-review the study. Any determination from the FDA on the status of the risk of the device will be final.

5) CPHS will not approve a clinical investigation using a banned device.

Emergency Use of Investigational Drugs and Devices

In very specific situations, the FDA will allow for the emergent use of investigational products (IP) (e.g., drugs, biologics, devices) without prospective IRB review and approval.

The following criteria must be met to comply with federal regulations for emergency use of unapproved drugs, biologics and devices.

1) The patient has a life-threatening condition that needs immediate treatment;
2) No generally acceptable alternative treatment for the condition exists; and
3) Because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

The FDA expects physicians to determine that a patient's circumstance meet the above criteria. The physician must also have substantial reason to believe that benefits gained will be substancial if the investigational product is used. Physicians should follow as many patient protection measures as possible including:

1) Seeking informed consent from the patient or a legal representative;
2) Clearance from the institution in which the IP is utilized as specified by their policies;
3) Concurrence of the Institutional Review Board (IRB)/CPHS chairperson;
4) An independent assessment from an uninvolved physician; and
5) Authorization from the device manufacturer.

The emergency use of an investigational product must be reported to the FDA and CPHS within five working days of use. The IDE Report (21 CFR 812.35(a)(2)) should include a summary of the patient's condition that warranted the use of IP in an emergency situation, the patient protections that were implemented and the outcome of the patient following use.

When possible, CPHS recommends the treating physician consult with the CPHS Chairperson or Vice Chairperson prior to using the investigational production emergency situations if time permits.

PIs should keep in mind that the emergency use of an investigational product is not part of a systematic investigation designed to develop or contribute to generalizable knowledge and thus does not require prospective review and approval by an IRB. Additionally, data generated from the emergent use of an investigational product should not be incorporated into a project that meets the definition of research.

CPHS does not review research that qualifies for the Emergency Exception from Informed Consent (i.e., EFIC trials) which is a special set of FDA regulations for Emergency Research (21 CFR 50.24). If you have questions regarding this, please contact the CPHS Office.

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Unanticipated Problems, Adverse Events, and Serious Adverse Events

This policy describes the requirements for identifying, reporting, reviewing, and managing **unanticipated problems (UAPs)**, including **unanticipated adverse device effects (UADEs)**, in human subjects research.

Federal regulation requires prompt reporting to CPHS for any UAPs. For the purposes of this policy, UAPs includes unanticipated adverse device effects (UADEs) and deaths of research participants.

This policy applies to all investigators and research staff conducting human subjects research under the oversight of CPHS, regardless of funding source or study location.

Investigators with IRB approval from CPHS must report UAPs within 10 (ten) working days after first learning of the UAP. In addition, investigators must report all UAPs to the reviewing IRB (and CPHS) when relying on an external IRB. In addition, UAPs and adverse events (AEs) must be summarized for CPHS in continuing review applications.

Failure of an investigator to follow any requirements of this policy may require CPHS to suspend or terminate the study and/or report noncompliance to appropriate entities that include, but are not limited to, government agencies, study sponsors, or other institutions involved in the research.

Definitions

1) **Adverse Events:** any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. AEs can be considered UAPs if all three (3) criteria for an UAP are met.

   Internal AEs are those experienced by participants enrolled at CalHHS sites or participants enrolled in studies where CalHHS or where a California state employee serves as the Principal Investigator.

   External AEs are those experienced by participants enrolled at sites external to CalHHS or where the Principal Investigator is not an employee of the state of California.

2) **Serious Adverse Event:** is any AE that results in death, is life threatening, results in participant hospitalization or prolongation of existing hospitalization, results in a persistent or significant disability/incapacity, results in a congenital anomaly/birth defect, or based upon appropriate medical judgement may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes in this definition.

3) **Unanticipated Problems:** Includes any incident, experience, or outcome which meets all of the following criteria:

a) It is "***unexpected***" in terms of its nature, severity, or frequency given 1) the research procedures described in the protocol-related documents, such as IRB-approved research protocol and informed consent document; and 2) the characteristics of the subject population being studied;

b) It is "***related***" or "***possibly related***" to the participation in the research; meaning there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; and

c) It suggests that the research ***places subjects or others at greater risk of harm*** (including physical, psychological, economic, or social harm) than was previously known or recognized.

For FDA-regulated research, any AEs observed during the study should only be considered a UAP if it is unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, or revisions to the informed consent or investigator's brochure). An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

Examples of an UAP include, but are not limited to, the following:

i) A breach of confidentiality or privacy that involves real or potential risk (e.g., unauthorized use or disclosure of protected health information);

ii) Data and safety monitoring reports or new literature that indicates the frequency or magnitude of harms or benefits may be different than initially presented to the IRB or previously understood;

iii) Incarceration of a research participant in a protocol not approved to enroll prisoners;

iv) Complaints from research participants or others involved in the research that indicate unexpected risks or cannot be resolved by the research team; and

v) Warning or determination letters issued by any funding agency or regulatory body including the Office of Human Research Protections (OHRP) or the Food and Drug Administration (FDA) that is in any way associated with the research approved by CPHS.

4) **Unanticipated Adverse Device Effect:** any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

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Procedures for UAP Review

1) The Principal Investigator is responsible for:
    a) **Assessing events** to determine whether they meet criteria for a UAP or UADE;
    b) **Promptly reporting** possible UAPs and UADEs to CPHS within ten working days of being identified;
    c) **Implementing immediate actions** to eliminate hazards to subjects when necessary, even prior to CPHS review (see Modifications policy for additional information);
    d) **Submitting follow-up information** to CPHS as additional details become available;
    e) **Submitting protocol amendments** when corrective actions result in permanent changes to the research; and
    f) **Cooperating with sponsors, coordinating centers, and other institutions**, as applicable.
2) In any instance where the study team suspects a UAP, AE, SAE, or UADE, the study team should ensure prompt review of this event takes place by the Principal Investigator. If the Principal Investigator is not available for any reason:
    a) A co-investigator may fulfill these requirements to meet any reporting requirements and timelines.
    b) If neither the Principal Investigator or co-investigator is available, the study team should contact CPHS for direction.
3) Principal investigators and study teams must submit suspected UAPs and UADEs to CPHS through the electronic IRB system.
4) When CPHS receives a report containing a suspected UAP or UADE, CPHS staff will screen the report to determine if additional information is required and will communicate with the study team to obtain any required information.
5) When all required information is available in the report, CPHS staff will assign the report to the CPHS Chair and Vice-Chair (or designee) for review. If the Chair or the Vice-Chair are not readily available to provide their review, a single review (or designee review) may be acceptable.
    a) The CPHS Chair and Vice-Chair will determine if the report meets the definition of a UAP or UADE.
        i) For any report that meets the definition of a UAP or UADE, the report will be assigned to the Full Board for review.
        ii) For any report which does not meet the definition of a UAP or UADE, the report will be acknowledged by the CPHS Chair and Vice-Chair. This decision will be communicated to the investigator describing the reasons why the report did not meet the definition of an UAP or UADE. The investigator may choose to provide additional details if appropriate or necessary.

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iii) If there is insufficient information for the CPHS Chair and Vice-Chair to determine if the report meets the definition of a UAP or UADE, the CPHS staff will be instructed to obtain additional details or clarifying information.

6) For any reports assigned to the full CPHS board for review, the board will:

   a) Consider whether the action plan provided in the report is adequate regarding:

      i) Actions taken to eliminate an immediate apparent hazard without prior IRB approval;

      ii) Other actions taken or planned by the PI, including changes to the consent, protocol, or other study document, notifications to appropriate agencies or institutions, etc.;

      iii) Considers whether additional actions or safeguards should be taken by the investigator to protect study participants;

      iv) Considers whether the affected research still meets the requirements for IRB approval under federal regulations and institutional policies; and/or

      v) Considers whether a suspension or termination of the study is necessary if the study no longer meets the requirements for IRB approval.

   b) The full board will communicate its determination to the investigator with any reasons justifying its decision and requests for additional information.

Timeline for Reporting

Reports to the Office of Human Research Protections (OHRP), the Food and Drug Administration (FDA) and other federal agencies will be made promptly in accordance with the policy for reporting to federal agencies. In the event a situation requires extended time (i.e., greater than 90 calendar days) to investigate or resolve, a preliminary report will be sent to the agency followed by a final report.

HIPAA Privacy Rule Regulations

HIPAA Privacy Rule and Privacy Board Authority

CPHS serves as a Privacy Board, as permitted under 45 CFR 164.512(i), for research involving Protected Health Information (PHI).

When research involves the use, disclosure, creation, receipt, maintenance, or transmission of PHI, CPHS will review the proposed activities to ensure compliance with the HIPAA Privacy Rule and applicable California privacy laws.

Researchers must either:

1. Obtain HIPAA authorization from participants;

2. Obtain a waiver or alteration of HIPAA authorization from CPHS acting as a Privacy Board; or
3. Demonstrate that another HIPAA-permitted pathway applies.

CPHS may approve HIPAA authorizations that are combined with informed consent documents as long as all elements of a valid authorization are contained in the document.

CPHS may approve a waiver or alteration of HIPAA authorization only when all regulatory criteria established by 45 CFR 164.512(i)(2) are satisfied.

When CPHS is serving solely under its IPA authority and not as an IRB, CPHS may still perform Privacy Board functions when PHI is involved.

Criteria for Waiver or Alteration of HIPAA Authorization

CPHS may waiver or alter HIPAA authorization when it determines that:

1) The use or disclosure of PHI involves no more than minimal risk to privacy because:
    a. An adequate plan exists to protect identifiers;
    b. An adequate plan exists to destroy identifiers when no longer needed; and
    c. Adequate written assurances exist against improper reuse or disclosure.
2) The research could not practicably be conducted without the waiver or alteration.
3) The research could not practicably be conducted without access to and use of the PHI.
4) Waiver determinations must be documented in:
    a. Reviewer checklists;
    b. Determination letters; and
    c. Convened meeting minutes when applicable.

Research Noncompliance

This policy outlines responsibilities for managing issues of noncompliance with human subjects regulations, CPHS requirements, institutional policies, and/or CPHS determinations.

Noncompliance, which appears to meet the definition of serious or continuing noncompliance (as defined below), with the regulations, institutional human research policies, and/or with the requirements or determinations of the Institutional Review Board (IRB) must be promptly reported to CPHS (even if relying on an external IRB).

Noncompliance that is determined to be serious or continuing must be promptly reported by CPHS to the appropriate state officials, other institutions, Federal Funding Agencies (if applicable), and the U.S. Food and Drug Administration (FDA) (if applicable).

Results of any internal or external audits that identify issues that appear to constitute serious or continuing noncompliance must be promptly reported to CPHS.

This policy applies to all investigators and research staff conducting human subjects research under the oversight of CPHS, regardless of funding source or study location.

Investigators with approval from CPHS to conduct human subjects research must provide an initial report of apparent serious and/or continuing noncompliance within two (2) working days after first learning of the event even if the investigator is still working to identify all relevant details. Investigators and CPHS will communicate as the inquiry proceeds until a final draft report of the event is prepared.

Investigators and study teams should contact CPHS in any situation where guidance on following the requirements of this policy is needed.

Examples of noncompliance can include but are not limited to:

1) Performing research activities such as consenting participants without first obtaining CPHS approval or a determination of exemption from the CPHS;
2) Deviating from or violating the provisions of the CPHS approved research or procedures;
3) Violation of institutional policies, state and local laws, federal regulations, and any conditions placed upon the review, oversight, or conduct of the research;
4) Permitting a CPHS-approved study to expire without stopping all research activities, including data analysis; and/or
5) Failure to obtain informed consent from research participants.

Minor noncompliance events (e.g., deviations) that do not meet CPHS definitions of serious noncompliance or continuing noncompliance do not require prompt reporting to CPHS. Instead, these events should be reported at continuing review or notice of study closure, whichever comes first. Although, when patterns emerge in minor events, these patterns may appear to constitute continuing noncompliance, which may or may not also be serious noncompliance, and therefore may require prompt reporting.

In addition, investigators must report all noncompliance to the reviewing IRB (and CPHS) when relying on an external IRB. In particular, noncompliance reporting requirements for IRBs other than CPHS may be different than those identified in this policy and investigators must report as per those policies to those external IRBs.

Failure of an investigator to follow any requirements of this policy may lead to CPHS to suspending/terminating the study and/or reporting noncompliance to appropriate entities that include, but are not limited to, government agencies, study sponsors, or other institutions involved in the research.

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Definitions

1) **Noncompliance:** The failure of a person or organization to act in accordance with the requirements of a law, regulation, policy, or the requirements and/or determination of an IRB.

   Internal noncompliance are events occurring at studies conducted at CalHHS sites or where a California state employee serves as the Principal Investigator.

   External noncompliance are those events occurring at sites external to CalHHS or where the Principal Investigator is not an employee of the state of California.

2) **Serious Noncompliance (SNC):** Noncompliance that materially increases risks or causes substantive harm to research participants or materially compromises the rights, safety, or welfare of participants (also referred to as **major deviations**), including consideration of the following:

   a) harm to participants;

   b) exposure of participants to a significant risk of substantive harm;

   c) compromised privacy and confidentiality of participants;

   d) willful or knowing research misconduct on the part of the investigator;

   e) a violation of ethical principles for human research; and/or

   f) damage caused to the scientific integrity of the data collected.

3) **Continuing Noncompliance (CNC):** Noncompliance that recurs after an investigator has been notified of a similar or related noncompliance concern pertaining to one or more protocols.

   This notification may be identified through internal monitoring, external monitoring, audits, or other means of notifying the investigator of the issue.

4) **Deviation (also Protocol Deviation):** Minor or administrative changes from the approved study protocol without prior CPHS approval that are generally noted or recognized after it occurs, or if identified before it occurs, cannot be prevented by the investigator (i.e., not an intentional deviation). Deviations have no potential substantive effect on the risks to research participants or the scientific integrity of the research plan or the value of the data collected. Deviations are limited to minor departures from the protocol for a single subject and do not result from willful or knowing misconduct on the part of the investigator(s).

Procedures for Noncompliance Receipt

Information alleging or revealing noncompliance in studies that enroll human participants may come to the attention of the CPHS through several pathways including:

1) initial submissions;

2) renewals/continuing review;
3) internal audits or monitoring;
4) Food and Drug Administration (FDA) audit or inspection reports (e.g., FDA form 483);
5) sponsor audit reports;
6) adverse event/safety reports/incident reports;
7) reports from collaborators, employees, or participants; or
8) any other sources.

For events known to the PI and/or study teams, submissions of apparent SNC or CNC must be made through the electronic IRB system to CPHS. The PI is responsible for:

1) Assessing events to determine whether they meet criteria for SNC or CNC;
2) Promptly reporting possible SNC or CNC to CPHS once identified;
3) Implementing immediate actions to eliminate hazards to subjects when necessary, even prior to CPHS approval;
4) Submitting follow-up information to CPHS as additional details become available;
5) Submitting protocol amendments when corrective actions result in permanent changes to the research; and
6) Cooperating with sponsors, coordinating centers, and other institutions, as applicable.

In any instance where the study team suspects SNC and/or CNC, the study team must ensure prompt review of the event by the PI. If the PI is not available for any reason, a co-investigator may fulfill these requirements to meet any reporting requirements and timelines. If neither the Principal Investigator nor co-investigator is available, the study team should contact CPHS for direction.

7) When CPHS receives a report containing apparent SNC or CNC, the CPHS Administrator will be notified. After notification, the CPHS Administrator and/or CPHS Chair will screen the report to determine if additional information is required and will communicate with the study team to obtain any required information. Care will be taken within the CPHS Office to maintain confidentiality.
8) Whenever necessary, CPHS will engage CalHHS legal representatives to invoke attorney-client privilege and obtain legal guidance.

Preliminary Determination to Suspend or Not Suspend the Research

The CPHS Administrator is responsible for the initial review of all noncompliance allegations, including reports of apparent SNC or CNC. Reports must contain enough information to determine whether the allegation or report is sufficiently credible and specific so that potential evidence of noncompliance may be identified and acted upon.

When all required information is available in the report, the CPHS Administrator will report all credible allegations or reports of noncompliance to the CPHS Chair and Vice-Chair and relevant agency representatives.

For allegations of noncompliance associated with research team members, the CPHS Administrator makes appropriate recommendations to the CPHS Chair regarding possible immediate suspension of the research or enrollment of participants. These individuals should also consider whether the suspension of all research is warranted. This initial decision to suspend research is based on preliminary review of available information, communication with the PI involved in the alleged noncompliance activities, and the seriousness of the allegations. The decision to suspend can be made by the convened CPHS or the CPHS Chair. If research activities are suspended, CPHS will report the suspension in accordance with federal regulations and applicable CPHS policies.

Any individual with a personal, professional, or financial conflict of interest must recuse themselves from the process of investigating the noncompliance and making recommendations.

Investigating Noncompliance

After the preliminary evaluation of the allegation, an investigation into the allegation is undertaken with the authority and oversight of the CPHS Administrator. The investigation is initiated within five (5) working days of the recognized concerns. The purpose of the investigation is fact-finding and may involve examination of study records and discussion with research personnel, research participants, witnesses, the individual reporting the allegation, or others.

The CPHS Administrator will communicate with and coordinate investigations with appropriate Agency representatives to the extent required by applicable Agency policies or state law.

Allegations that include issues that rise to the level of potential research misconduct (i.e., fabrication or falsification of data or plagiarism) will be reported to the Responsible Official and the Research Integrity Officer (if applicable) for further review and potential investigation in accordance with Agency policy, state law and the federal regulations.

Resolution of the Investigation

The CPHS Administrator and CPHS Chair will determine if the report meets the definition of SNC or CNC and there is sufficient evidence that the event is rooted in fact or that the allegation is credible.

For any report that meets the definition of SNC or CNC, the report will be assigned to the Full Board for review.

For any report which does not meet the definition of SNC or CNC, the report will acknowledged by the CPHS Administrator or CPHS Chair. This decision will be communicated to the investigator describing the reasons why the report did not meet the definition of SNC or CNC. The investigator may choose to provide additional details if appropriate or necessary.

For any reports assigned to the full board for review, CPHS may take the following actions:

1) Determine that additional investigation is needed. Should this occur, CPHS can appoint a subcommittee to investigate the allegations further. The subcommittee will then communicate any additional information or findings to the convened CPHS at a subsequent meeting;
2) Determine that no action is required;
3) Suspend enrollment and/or all research activity for the research in question (in accordance with the Suspension and Termination of IRB approval policy);
4) Terminate the research (in accordance with the Suspension and Termination of Research policy);
5) Require a response from the investigator with a plan for corrective action and a proposed timeline for ensure compliance within a specific timeframe;
6) Recommend to the Secretary of CalHHS that an investigator or institution/organization be restricted in some or all future submissions to CPHS for review and approval under all authorities of CPHS.
7) Initiate audits or monitoring of all or part of the PI's active protocols;
8) Request the PI modify the research protocol;
9) Require retraining of the PI and/or research personnel;
10) Require modification of the information disclosed during the consent process;
11) Require additional information be provided to past or current participants;
12) Require modification of the renewal schedule for the research (i.e., more often than annual);
13) Communicate with other IRBs or institutions involved with the research, as applicable, which may include requests for additional investigation or fact-finding activities;
14) Require current participants be informed and possibly undergo the informed consent process again when information might relate to the participant's willingness to continue to participate in the research;
15) Monitoring of the consent process; and/or
16) Take any other action deemed appropriate by CPHS.

Timeline for Reporting

Reports to the Office of Human Research Protections (OHRP), the Food and Drug Administration (FDA) and other federal agencies must be made promptly in accordance with the policy for reporting to federal agencies. In the event a situation requires extended time (i.e., greater than 90 calendar days) to investigate or resolve, a preliminary report will be sent to the agency followed by a final report.

IRB Noncompliance

Noncompliance on the part of CPHS with federal regulation, state law, and/or CPHS policy is initially reported to and reviewed by the Chief Data and AI Officer. If identified by CPHS staff or members, this will be escalated to the CPHS Administrator for review and assessment. If it is determined to be potential CPHS noncompliance, the CPHS Administrator will escalate to the Chief Data and AI Officer.

The Chief Data and AI Officer may convene an ad hoc committee to review the noncompliance and make the appropriate determinations. If convened, the ad hoc committee shall include at least 3 individuals, which can include a member of the IRB, the Chief Compliance Officer, a consultant, Agency leadership, or other individuals with appropriate expertise and experience to make the necessary determinations.

CPHS, or IRB, noncompliance can include but is not limited to:

1) Failure of the IRB to document in its meeting minutes or supporting documents specific findings such as a waiver of the requirement to obtain informed consent from participants.
2) Failure to document determinations for approval of research and/or specific determinations required for vulnerable populations.
3) Misappropriation of categories for exempt determinations or review by expedited procedures.
4) Conduct of a meeting where quorum was lost (e.g., a non-scientific member was not present) or reviewing an agenda item where CPHS lacked appropriate expertise to evaluate the research (and failed to obtain a consultant's expertise to supplement the IRB review).
5) Failure of CPHS to comply with the Bagley-Keene Act by holding a private or exclusive meeting; failure to provide adequate notice with an agenda; or conducting serial meetings to discuss, vote, or develop concurrence on items under CPHS jurisdiction outside of a public meeting.

Determinations of noncompliance on the part of the IRB will be reported to the Agency Secretary and the convened IRB as information. Processes for programmatic improvements are the responsibility of the CPHS Administrator. Determinations of serious noncompliance on the part of the IRB will be reported to the federal agencies in accordance with federal policy, as applicable.

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Suspension and Termination of Research

This policy describes the procedures for documenting the requirements for when CPHS suspends or terminates an approved research project.

Federal regulations allow CPHS to suspend or terminate human subject research (45 CFR 46.113/ 21 CFR 56.113).

1) CPHS may suspend or terminate approval when research is not being conducted in accordance with IRB requirements or has been associated with unexpected serious harm to participants.
2) In addition to CPHS, other California HHS officials, such as the Institutional Official (IO), CPHS Chair or Vice-Chair, and CPHS Administrator may suspend research.
3) During the suspension of a study, all research activities must cease.
4) Only the convened IRB may terminate research.
5) If suspension or termination of CPHS approval occurs, the reporting of the suspension or termination will be in accordance with applicable regulations (45 CFR 46.113/21 CFR 56.113) and CPHS policies.

Suspension or Termination by CPHS

1) CPHS is authorized under federal regulations to suspend or terminate approval of research that is not being conducted in accordance with IRB policies and procedures or has been associated with unexpected serious harm to participants.
2) Reasons CPHS may suspend approved research include, but is not limited to, the following:
    a. A principal investigator (PI) fails to provide CPHS with information requested that can affect the safety, rights, and welfare of participants.
    b. New information about the research becomes available that could alter the determinations made by CPHS at initial review or renewal of the research.
    c. The PI fails to comply with federal, state or local laws or regulations, and/or institutional policies regarding the conduct of research involving human participants.
    d. The PI fails to meet the stipulations imposed by CPHS at renewal within the timeframe designated by CPHS.
    e. During an investigation of an allegation of noncompliance or to evaluate a safety issue.
3) Notification of suspension or termination of CPHS approved research must include the reason for the IRB's action and shall be reported promptly, when applicable, to the PI and appropriate officials (including the Institutional Official). CPHS will follow the policy

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for reporting suspension or termination of research to Office for Human Research Protections, the Food and Drug Administration, or any applicable federal funding agency, as appropriate.

4) CPHS shall determine and inform the PI of steps to be taken due to suspension or termination of the research, which may include:

    a. Notifying current participants that the study has been suspended or terminated by communications that will be reviewed and approved by CPHS.

    b. Presenting to CPHS procedures for withdrawal or transferring of participants to another site that is participating in the research that will consider the rights and welfare of those individuals.

    c. Informing the participants of any follow-up procedures permitted or required by CPHS for their safety.

    d. Reporting to CPHS and the sponsor of any adverse events or outcomes that happen during the follow-up period.

5) The communication from CPHS to the PI will explain the circumstances of the suspension or termination and provide the PI an opportunity to respond. The communication will ask the PI to provide a plan for ensuring that the rights and welfare of all currently enrolled, or previously enrolled participants, if appropriate, are protected.

6) All suspensions and terminations of research will be documented in the electronic IRB system. Decisions made by the convened IRB to suspend or terminate research will be documented in the meeting minutes.

7) To lift the suspension, the PI must satisfactorily resolve any pending issues identified by CPHS. If the issues have not been resolved after 60 calendar days, the study will be terminated. Exceptions can be made to this requirement upon determination by the CPHS Administrator.

8) To reinstate a project that has been terminated, the investigator must submit the research to CPHS as a new submission, and all issues identified from the previous study must be resolved to the satisfaction of the CPHS IRB.

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Reporting to Regulatory Agencies & Sponsors Regarding Research Involving Human Participants

The purpose of this policy is to establish guidelines to ensure CPHS meets its reporting obligations when reporting to federal agencies is required.

The CPHS Institutional Official (IO) will ensure that full, accurate, and timely reports are submitted to the appropriate regulatory agencies when required.

The following procedures will be utilized when reporting to regulatory agencies or sponsors is required:

1) Prompt reporting of the following is required by federal regulations (45 CFR § 46.108(a)(4), 45 CFR § 46.113, and 21 CFR § 56.113):
    a) suspension or termination of previously approved research, regardless of the reason;
    b) serious or continuing noncompliance with the federal regulations or determinations of CPHS; and/or
    c) unanticipated problems involving risks to participants and others.
3) The CPHS Administrator is responsible for drafting the report that will be submitted to the relevant federal agencies.
    a) When reporting to OHRP is required, CPHS will follow the guidance entitled "Reporting Incidents to OHRP (2022)" and "OHRP Incident Report Form Instructions."
    b) For research that is regulated by the Food and Drug Administration (FDA), a letter outlining the incident will be drafted by the CPHS Administrator. The IO is responsible for reviewing and signing the letter which will be sent to the FDA by the CPHS Administrator within fifteen (15) working days following the actions taken by CPHS. The FDA website contains information on where to send the correspondence. The letter will include the following information:
        i) the category of the incident (e.g., non-compliance, unanticipated problem);
        ii) IND or IDE number, as applicable;
        iii) full title of the research protocol;
        iv) name(s) of the clinical investigator(s) (i.e., Principal Investigator and any Sub-investigators);
        v) name of the research sponsor or sponsor-investigator;
        vi) a detailed description of the incident;
        vii) corrective action plan;
        viii) IRB determinations; and

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ix) name and contact information for the IO and CPHS Administrator

4) The PI or Responsible Official must provide a copy of the report to project sponsors (federal state, foundation or private), as applicable, and provide confirmation to CPHS of the notification.

5) A copy of the letter should also be sent to:

   a) CalHHS Office of Technology and Solutions Integration Legal Division

   b) The PI and Responsible Official of the study

   c) The IRB of record (if CPHS is not the IRB of record)

   d) The IO of the institution with which the PI is affiliated, as applicable

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Appendix A: Acroynms

AE	Adverse Event
DHHS	Department of Health and Human Services
COI	Conflict of Interest
DUA	Data Use Agreement
FCOI	Financial Conflict of Interest
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HHS	Health and Human Services
HPA	Human Protections Administrator
HRPP	Human Research Protection Program
HUD	Humanitarian Use Device
IDE	Investigational Device Exemption
IO	Institutional Official
IRB	Institutional Review Board
LAR	Legally Authorized Representative
MP	Management Plan
NHSR	Non-Human Subjects Research
NSR	Non-Significant Risk (Device)
OHRP	Office for Human Research Protections
PI	Principal Investigator
SR	Significant Risk (Device)
UAP	Unanticipated Problems Involving Risks to Subjects and Others

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Appendix B: Glossary of Terms

Adverse Event	Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. AEs can be considered UAPs if all three (3) criteria for an UAP are met. ***Internal AEs*** are those experienced by participants enrolled at CalHHS sites or participants enrolled in studies where CalHHS or where a California state employee serves as the Principal Investigator. ***External AEs*** are those experienced by participants enrolled at sites external to CalHHS or where the Principal Investigator is not an employee of the state of California.
Assent	***Assent*** means when a child affirmatively agrees, either orally or in writing, to participate in research. Acquiescence is not evidence of assent.
Authorized Organizational Officials	***Authorized organizational officials*** are those individuals authorized by the institution to suspend IRB approved research. Those individuals include the Institutional Official or the IRB Chair.
Children	***Children*** are persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction where the research will be conducted (in California, individuals younger than 18 years old are considered children).
Clinical Investigation	Any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit
Coercion	***Coercion*** is when someone uses a credible threat of harm or force to control another person.
Cognitively Impaired	***Cognitively impaired*** means having a psychiatric disorder (e.g., psychosis, neurosis, personality, or behavior disorders), an organic impairment (e.g., stroke, dementia, delirium), or a developmental disorder

	(e.g., mental retardation) that affects cognitive or emotional functions to the extent that an individual's capacity to make judgements through reasoning is significantly diminished.
Continuing noncompliance	Noncompliance that recurs after an investigator has been notified of a similar or related noncompliance concern pertaining to one or more protocols. This notification may be identified through internal monitoring, external monitoring, audits, or other means of notifying the investigator of the issue.
Controverted Issues	Issues that cause controversy and dispute among the CPHS membership during a convened meeting. Controverted issues that arise during a meeting may be the result of opposition to some aspect of the proposed research or may regard applicability or interpretation of ethics or regulations.
Deception	***Deception*** involves misleading participants as to the true nature of the study. There are typically four general categories of deception in research involving human participants. ○ ***Outright deception*** *(sometimes referred to as active deception)* is where researchers inform individuals that they are participating in research; however, the participant is provided false or misleading information regarding the true purpose of the study. In other words, they are unaware of the deception. ○ ***Covert deception*** is where researchers have individuals participate in research without being aware of their participation. ○ ***Incomplete disclosure*** is where an investigator withholds information about the specific purpose, nature, or other aspect of the research ○ ***Authorized deception*** is where the researchers withhold information or mislead individuals who agree to be ignorant or deceived about the true purpose of the research.
Decisional Impairment	***Decisional impairment*** means that individuals have a diminished capacity to understand information, reason through it, and then make decisions because of a disorder that affects either cognitive or emotional functions.

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	• Other individuals may have decisional impairment because they suffer from a degenerative disease that affects their processing of information and decision-making capacity. • Readers should be advised that the terms decisional impairment and diminished decisional capacity are frequently used interchangeably.
Device	***Device*** is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, software application (e.g., for a phone or tablet), or other similar or related article, including a component part or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.
Deviation	Minor or administrative changes from the approved study protocol without prior IRB approval that are generally noted or recognized after it occurs, or if identified before it occurs, cannot be prevented by the investigator (i.e., not an intentional deviation). Deviations have no potential substantive effect on the risks to research participants or the scientific integrity of the research plan or the value of the data collected. Deviations are limited to minor departures from the protocol for a single subject and do not result from willful or knowing misconduct on the part of the investigator(s).
Economically or Educationally Disadvantaged Individuals	***Economically or educationally disadvantaged individuals*** who, by virtue of their socioeconomic and/or educational background, are disadvantaged, and therefore have a special risk. When these individuals participate in research, they may be more susceptible to coercion or undue influence.
Expedited Review	An ***expedited review*** procedure consists of a review of research involving human participants by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.
Guardian	***Guardian*** means an individual who is authorized under applicable state or local law to consent on behalf of a child.

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Human Subject / Human Participant	***Human subject*** means a living individual about whom an investigator (whether professional or student) conducting research (45 CFR 46.102(e)(1)): ○ Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens (45 CFR 46.102(e)(1)(i)); or ○ Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens (45 CFR 46.102(e)(1)(ii)). • Readers should be advised that when the term ***participant*** is used in this policy document it refers to individuals who voluntarily participate as human subjects in research. This choice to use ***participant*** instead of "subjects" has been determined solely by stylistic preference and does not override how the federal regulations have defined human subject.
Incompetence	***Incompetence*** is a legal term meaning inability to manage one's own affairs. It is often used as a synonym for incapacity.
Investigation	A clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device
Investigational Device Exemption	***Investigational device exemption*** *(IDE)* is an allowance from the Food and Drug Administration (FDA) for the use of an investigational device in a clinical study in order to collect safety and effectiveness data
Investigator	An individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team
Institutional Review Board	***IRB*** means an institutional review board established in accordance with and for the purposes outlined in the federal regulations at 45 CFR 46 and 21 CFR 56.
Institutional Review Board Chair(s)	Individuals chosen from IRB members who will typically be staff of CalHHS, knowledgeable in human subjects research, including the federal and state regulations, agency policies, and ethics relevant to such research. The IRB Chairs shall preside over and be authorized to speak for the IRB.

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Legally Authorized Representative (LAR)	***Legally authorized representative*** (LAR), in relation to research involving human participants, means "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research" (45 CFR 46.102(i), 21 CFR 50.3(1)).
Minimal Risk	***Minimal risk*** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(j)).
Monitoring/Post Approval Monitoring (PAM)	an ongoing process usually directed by management to ensure processes are working as intended.
Noncompliance	Failure of a person or organization to act in accordance with the requirements of a law, regulation, policy, or the requirements and/or determination of an IRB. ***Internal noncompliance*** are events occurring at studies conducted at CalHHS sites or where a California state employee serves as the Principal Investigator. ***External noncompliance*** are those events occurring at sites external to CalHHS or where the Principal Investigator is not an employee of the state of California.
Noninvasive	when applied to a diagnostic device or procedure, means one that does not by design or intention: a. Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or b. enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. For purposes of this policy, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive. (21 CFR 812.3(k))
Nonsignificant Risk Device	***Nonsignificant risk device*** does not meet the definition of a significant risk device. It only requires IRB approval prior to initiation of a clinical study.

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Parent	***Parent*** means a child's biological or adoptive parent.
Parental Permission	***Parental permission*** means that parent(s) or guardian(s) have agreed to allow their child or ward to participate in research.
Research	***Research*** means 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 (45 CFR 46.102(l)). ***Research (clinical investigation per FDA)*** means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms *research, clinical research, clinical study, study,* and *clinical investigation* are deemed to be synonymous (21 CFR 56.102(c)). ***Research (clinical trial per NIH)*** is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
Serious Adverse Event	is any AE that results in death, is life threatening, results in participant hospitalization or prolongation of existing hospitalization, results in a persistent or significant disability/incapacity, results in a congenital anomaly/birth defect, or based upon appropriate medical judgement may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes in this definition.
Serious noncompliance	Noncompliance that materially increases risks or causes substantive harm to research participants or materially compromises the rights, safety, or welfare of participants, including consideration of the following: a. Harm to participants; b. Exposure of participants to a significant risk of substantive harm;

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	c. Compromised privacy and confidentiality of participants; d. Willful or knowing research misconduct on the part of the investigator; e. A violation of ethical principles for human research; or f. Damage caused to the scientific integrity of the data collected.
Significant Risk Device	***Significant risk device*** means an investigational device that: ○ Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a participant; ○ Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a participant; ○ Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a participant; or ○ Otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.
Sponsor	A person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.
Sponsor-Investigator	An individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under FDA regulations include those of an investigator and those of a sponsor.
Subject	a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease
Suspension	***Suspension*** is an action where all or some of the research activities must stop until issues have been satisfactorily resolved. Suspended projects

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	still have IRB approval. Note that suspensions issued by the IRB are reportable to federal agencies.
Termination	***Termination*** is an action issued by the convened IRB that all or some of the research must stop permanently except for the continuation of follow-up activities necessary to protect the participants' safety.
Test article	any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.
Unanticipated Problem	Includes any incident, experience, or outcome which meets ***all of the following criteria:*** d) It is "***unexpected***" in terms of its nature, severity, or frequency given 1) the research procedures described in the protocol-related documents, such as IRB-approved research protocol and informed consent document; and 2) the characteristics of the subject population being studied; e) It is "***related***" or "***possibly related***" to the participation in the research; meaning there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; and f) It suggests that the research ***places subjects or others at greater risk of harm*** (including physical, psychological, economic, or social harm) than was previously known or recognized.
Undue Influence	***Undue influence*** is when someone misuses a position of power, of confidence, or of trust to exercise influence over others so they make decisions they would not otherwise make.
Vulnerable Populations	***Vulnerable populations*** are certain groups of participants who enroll in research that may be more vulnerable to undue influence or coercion. These participants may require additional protections and safeguards when they participate in research. Examples of vulnerable populations include children, prisoners, individuals with impaired decision-making capacity, or participants in circumstances that would make them vulnerable (e.g., students, employees, or economically or educationally disadvantaged persons).
Wards	***Wards*** are children in the care or custody of the state, courts, or any other agency, institution, or entity.

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Appendix C: Allowable Research Involving Children

ALLOWABLE RESEARCH INVOLVING CHILDREN			
45 CFR 46 (OHRP); 21 CFR 50 (FDA)	**CATEGORY**	**REQUIREMENTS** The IRB must determine the following before children may be involved as participants in research:	**PARENTAL PERMISSION**
46.404; 50.51	Research not involving greater than minimal risk	Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 46.408 and 50.55. **Wards of State**: There are not any additional regulatory protections to apply when wards of state enroll in research that the IRB has approved under this category.	Permission from one parent may be sufficient **Wards of State**: States may stand in *loco parentis*
46.405; 50.52	Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects	a. The risk is justified by the anticipated benefit to the subjects; b. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and c. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 46.408 and 50.55. **Wards of State**: There are not any additional regulatory protections to apply when wards of state enroll in research that the IRB has approved under this category.	Permission from one parent may be sufficient **Wards of State**: States may stand in *loco parentis*
46.406; 50.53	Research involving greater than minimal risk and no prospect of direct benefit to individual participants, but likely to yield generalizable knowledge about the participant's	a. The risk represents a minor increase over minimal risk; b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations; c. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and d. Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in 46.408 and 50.55. **Wards of State**: The IRB may approve research under this category if the research is either related to their status as wards; or conducted in schools, camps, hospitals, institutions, or	Permission must be obtained from both parents

	disorder or condition	similar settings in which the majority of children involved as children are not wards. The IRB must request that an advocate be appointed for each child who is a ward. The advocate will serve in addition to any other individual acting on behalf of the child as guardian.	
46.407; 50.54	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children	a. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and b. The Secretary of DHHS or Commissioner of Food and Drugs for the FDA, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either: 1. That the research in fact satisfies the conditions of 46.404 and 50.51, 46.405 and 50.52, or 46.406 and 50.53, as applicable, OR 2. The following: i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children; ii. The research will be conducted in accordance with sound ethical principles; iii. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 46.408 and 50.55. **Wards of State**: The IRB may approve research under this category if the research is either related to their status as wards; or conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as children are not wards. The IRB must request that an advocate be appointed for each child who is a ward. The advocate will serve in addition to any other individual acting on behalf of the child as guardian.	Permission must be obtained from both parents

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