

Case Western Reserve University

Cancer IRB

Standard Operating Procedures

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Introduction

Authority Under Which the IRB is Established and Empowered (45 CFR 46.103) (21 CFR 56.109(a))

The Case Cancer Institutional Review Board (“the Board” or “Case Cancer IRB”) is a standing Board of Case Western Reserve University (hereinafter called the “Institution” or “Case”). The Board acts under the authority of the Provost of Case University (the “Institutional Official”). The Board was established pursuant to Case’s supplemental application with the National Cancer Institute (hereinafter called “NCI”) to expand Cancer Center Support Grant No. CA043703 (the “Grant”) among Case and University Hospitals of Cleveland (hereinafter called “UHC”), to include the Cleveland Clinic Foundation (hereinafter called “CCF”) as stated in the September 22, 2003 letter to NCI signed by the Presidents of the three institutions.

“Cancer Research” is defined broadly by the Centers Branch of the NCI in its Guidelines¹, as “*research across a broad spectrum of scientific and medical concerns relevant to cancer.*” It includes “*all areas of research, including laboratory, clinical, prevention, control, behavioral, and population research.*”

Clinical and laboratory research. The Data Safety and Monitoring Plan (DSMP), submitted to the NCI and approved by them, defines clinical research as “*clinical trials for all phases of clinical therapeutic intervention, including behavioral clinical trials and diagnostic trials that involve therapeutic intervention or medical decision-making that impact on treatment of patients with cancer.*” The DSMP lists these trials as Phase I Clinical Trials, Phase II Clinical Trials, Phase III Clinical Trials, Stem Cell Therapy, Gene Transfer Studies, Behavioral Clinical Trials, and Multicenter Trials. The NCI Guidelines elaborate that clinical studies “*should involve relevant laboratory research whenever possible...fostering translation between laboratory and clinic.*”

Prevention, control, behavioral, and population research. The NCI Guidelines define cancer control research as “*the conduct of basic and applied research in the behavioral, social, and population sciences that, either independently or in combination with biomedical approaches, reduces cancer risk, incidence, morbidity, and mortality. The scope of this research is extensive, including pre-intervention behavioral and bio-behavioral research, randomized clinical trials involving healthy populations or survivors, to research focusing on dissemination and diffusion of effective medical and behavioral therapies. Prevention research is directed at healthy populations, including those at high risk and/or those with detectable precancerous lesions, and cancer survivors.*”

The Board is registered as an institutional review board (IRB) for Cancer Research with the Office for Human Research Protection (“OHRP”) (IRB Registration Number IRB00004924 under the Case Federalwide Assurance (FWA00004428) and is also listed as an IRB of record for cancer research involving human subjects, tissue and/or data (collectively, “Human Subjects”) conducted by cancer investigators recognized by Case, CCF and UHC (collectively, “Cancer Investigators”) under the UHC (FWA 00003937) and the CCF (FWA 00005367)

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assurances. As such, the Board is required to comply with the terms, conditions, and standards of those FWAs as well, but will cite and act under authority of the Case Federalwide Assurance (FWA 00004428). CCF and UHC will rely upon the review of the Case Cancer IRB as another qualified IRB within the meaning of 45 CFR 46.114 and 21 CFR 56.114. In the future, **after consultation with and written approval by UHC and CCF**, the Case Cancer IRB may also become an IRB of record for Case's other affiliates – the MetroHealth System (hereinafter "Metro").

Purpose of the Board

The Case Cancer IRB is formally designated to review and monitor Cancer Research involving Human Subjects to protect their rights and welfare in accordance with all applicable laws, regulations and ethical standards. The Case Cancer IRB also provides oversight and monitoring of such protections in accordance with the Common Rule and agrees that all Cancer Research submitted to the Case Cancer IRB shall be governed by the Common Rule (regardless of the source of support or funding) in addition to any other applicable laws. The Case Cancer IRB has responsibility for approving, requiring modification (to secure approval), or disapproving Cancer Research involving Human Subjects by Cancer Investigators and such other actions permitted of IRBs by law (45 CFR 46.109 and 21 CFR 56.109). The Cancer IRB also serves as the Case Cancer Research Privacy Board ("RPB") responsible for Case's compliance with and ensuring compliance with all Health Insurance Portability and Accountability Act regulations and guidance ("HIPAA") as set forth in the "Memorandum of Understanding concerning HIPAA Compliance Concerning Case Cancer IRB," as amended, which is incorporated by reference.

The Board has adopted these Standard Operating Procedures (Procedures" or "Written Procedures") to comply with the United States Department of Health and Human Services (DHHS) Regulations on all research with Human Subjects, the United States Food and Drug Administration (FDA) Regulations on research with Human Subjects and, when applicable, the International Conference on Harmonization (ICH) "Guidance for Industry- E6 Good Clinical Practice: Consolidated Guideline" and all other applicable laws, regulations and standards, including Joint Commission on Accreditation of Healthcare Organizations (JCAHO), CCF, and UHC policies, all of which, as amended, are incorporated herein.

The ethical conduct of research is a shared responsibility requiring cooperation, collaboration and trust among Case, UHC, and CCF administrators, investigators, and their research staff, the subjects who enroll in research, and the Case Cancer IRB members and support staff.

Statement of Ethical Principles

The Board is guided by ethical principles regarding all research involving humans as subjects as set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, entitled, The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.

The Board subscribes to the basic generally accepted principles governing research, as outlined in the Belmont Report: Respect for Persons, Justice, and Beneficence.

The ethical guidelines of the Belmont Report are considered in the review of all research activities, including informed consent, risk/benefit analysis and the selection of subjects for research. The Board strives to maintain sensitivity to community attitudes and to take into consideration the racial and cultural backgrounds of research subjects.

Authority of the Board

Scope of Authority Defined

Under the terms of the Case Federalwide Assurance entered into with the DHHS OHRP, the Board has the authority to protect all Human Subjects involved in Cancer Research conducted by Cancer Investigators at Case, CCF, or UHC if one or more of the following apply:

1. The Cancer Research is sponsored by any or all the institutions, or
2. The Cancer Research is conducted by any or all the institutions or under the direction of any employee or agent of any of the institutions in connection with his or her institutional responsibilities, or
3. The Cancer Research is conducted by or under the direction of any employee or agent of any of the institutions using any property or facility of the institution or
4. The Cancer Research involves the use of any of the institutions' non-public information to identify or contact human research subjects or prospective subjects.

The Case Cancer IRB, with the concurrence of all institutions, may assign a protocol to another IRB, either internal (i.e. to CCF or UHC IRB) or external, if it is determined that doing so serves the best interests of the Human Subjects or Case, CCF and UHC and in all cases is approved in writing in advance by the Case Cancer IRB.

Authority of the Board to Act on Proposed Cancer Research

The Board has authority to approve, require modifications in (to secure approval) or disapprove Cancer Research activities involving Human Subjects by Cancer Investigators.

The bases for these authorities are as follows DHHS regulations pertaining to rights and welfare of subjects and/or patients. 45 CFR Part 46 and U.S. FDA regulations pertaining to rights and welfare of human subjects and/or patients participating in research involving investigational drugs, devices or biologics. 21 CFR Parts 50, 56, 312 and 812.

Authority to Require Progress Reports and to Oversee Cancer Research

The Board has the responsibility and the authority to review progress of Cancer Research studies at least yearly and more often when appropriate. The Board also has the authority to observe or have a third party whom the Board determines is qualified and appropriate observe the consent process or any aspect of the Cancer Research in accordance with policies applicable to the institution where the clinical Cancer Research activity is physically conducted.

Authority to Suspend or Terminate Approval of Research

The Board has the responsibility and the authority to suspend or terminate approval of any Cancer Research that has an unanticipated problem involving risks to Human Subjects, serious or continuing noncompliance with applicable federal regulation or serious or continuing noncompliance with the requirements or determinations of the IRB.

Written notice of such action shall be provided in writing to the Institutional Official; the Human Protections Administrators of Case, CCF and UHC; and OHRP and FDA (as applicable).

Authority to Restrict Cancer Research

The Board has the responsibility and the authority to restrict any Cancer Research involving Human Subjects that it determines to warrant such restriction. If one aspect of a study fails to comply with federal regulations or Board requirements or determinations, the Board must restrict the study so as to restrict the portion found in noncompliance until it is brought into compliance.

Board Relationships

Administration of the Institution

The Chairperson of the Board, in that capacity, reports directly to the Dean of the Medical School, who reports to the Provost of Case on IRB matters. Under the terms of their FWAs, the Chair also reports on IRB matters to the Provost and Chief Academic Officer of CCF and the President and CEO of UHC.

Local IRB System and the IRB Advisory Committee

The local IRB system is comprised of five financially separate institutions: Case, UHC, CCF, Metro, and the Stokes VA. The IRB Advisory Committee (IAC) was created so that faculty, staff, and students of the five institutions would have coordinated education, training and auditing programs.

In accordance with federal requirements, our multiple project assurance has been replaced (April, 2003) by separate Federalwide Assurances. However, it is important to note that this does not effect the IRB process for reviewing protocols and other required educational activities.

Relationship between the Protocol Review and Monitoring System (“PRMS”) and the Case Cancer IRB

As stated in the policies and guidelines relating to the Cancer Center Support Grant (Section 9.4), the role of the PRMS is to review scientific merit, scientific priorities, and the scientific progress of the clinical protocol research of the center. This review is complementary to the role of the IRB as outlined in 45 CFR 46.111 and 21 CFR 56.111.

The primary responsibility of the Cancer IRB in reviewing a clinical study is to assure that the risks to subjects are minimized and reasonable in relation to anticipated benefits and that there are appropriate measures in place to provide for subject safety. While both committees may review the same materials and ask similar questions of the investigators, the intent of the review is different in that the PRMS is concerned with scientific merit and the IRB is charged with reviewing the risk and safety of the trial as it relates to the protections of research subjects.

The Case Cancer IRB members must be provided access to all relevant materials that describe the study or will be presented to the research subject including the protocol, consent, investigator brochure, questionnaires, diaries, and etcetera. However, the expertise of the PRMS committee will inform the IRB membership through the communication of excerpts from the PRMS minutes as to the statistical and scientific soundness of the protocol design. The IRB will also benefit from the PRMS review of the extent to which the protocol utilizes procedures already being performed on the subjects for diagnostic or treatment purposes.

In their review, the PRMS can provide advice to investigators on ways to improve the consent form. This advice should be given with the clear understanding that the IRB makes the final determination of the appropriateness of the consent form.

Other Committees and Department Chairpersons within the Institution, Including the Exempt Research Process

The Board is a standing committee of Case, which is independent of any other Committee, Department or Division of Case, CCF, and UHC. The Board shall require Cancer Research projects involving Human Subjects by Cancer Investigators to be reviewed and approved by Case and other appropriate Conflict of Interest Committee, Radiation Safety Committee, the Biosafety Committee and/or other regulatory committees of the affected institutions) as a condition of approval. It is the responsibility of the Board and the affected institutions' Institutional Officials to ensure that the determinations of the Board are followed.

The institutions may disapprove Cancer Research approved by the Board. However, the institutions, their departments, divisions and committees may not approve Cancer Research that has been disapproved by the Board. The Board will be notified in writing by the appropriate Human Protections Administrator of any such disapproval.

The Chairperson or his designee will make evaluations to determine if research is exempt from the federal regulations for the protection of human subjects. If a determination is made that the research is not exempt, the Cancer Research is required be submitted to the Case Cancer IRB for review. Exempt Cancer Research studies will be registered with the Case Cancer IRB and a written notice of such determination shall be provided to the Human Protections Administrator at each institution.

Cancer Research Investigators

Only faculty, fellows, staff and others determined eligible by the Cancer IRB and by Case, CCF, or UHC to perform Cancer Research may serve as Principal Investigators on cancer protocols at its respective institution. The Board recognizes only one Principal Investigator for each Cancer Research project. The Principal Investigator has ultimate responsibility for his/her Cancer Research project and all official Board correspondence is addressed to the Principal Investigator. No Cancer Research studies involving Human Subjects may be conducted without Case Cancer IRB approval. Case faculty members, employees, staff and students properly licensed, qualified, insured and determined eligible by the Case IRB and by CCF or UHC, if applicable, to perform Cancer Research may act as Sub-Investigators at its respective institution.

All Cancer Investigators (whether Principal Investigators or Sub-Investigators) and all study personnel engaged in the human subject aspects of the research will complete the University of Miami Collaborative IRB Training Initiative course (<http://www.miami.edu/citireg>) on Human Subject Protections or meet the institutional requirement for training deemed appropriate by the institution at which they will perform the Cancer Research activity. All investigators shall comply with all applicable laws, JCAHO and hospital policies, grants and contracts in

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connection with the Cancer Research. Case Cancer IRB staff will determine prior to Board Review that such requirements have been met.

Student Research

A Case faculty member assigning research projects involving Human subjects shall take an active role in assuring that the human subjects of student research are adequately protected. Case requires that faculty advisors (“Responsible Investigators”) take an active part in preparing students for the role of researcher, instructing them in the ethical and legal conduct of research and assisting in the preparation of IRB applications. After protocol approval, the Responsible Investigator shall meet regularly with the student in order to review their work and progress. While a student may serve as the Principal Investigator for the protocol, the Responsible Investigator is ultimately responsible for the protection of human subjects. A faculty member’s signature on the application indicates his/her willingness to comply with all administrative and federal regulations, University Policy on the Involvement of Human Participants in Research, and all grants, contracts, and policies and procedures of Case, CCF or UHC where the research activity is conducted. To comply with this policy, the faculty member who is acting as the Responsible Investigator is required to educate and mentor the research team, but is also responsible for maintaining research records as required by law, University policy, and the policies of CCF and UHC, as appropriate.

Other Institutions

The Board may act in liaison with the IRBs of other institutions as necessary to assist in the approval of joint and cooperative Cancer Research projects involving multiple sites and/or investigators. Subject to the terms of prior written approval by the Human Protections Administrator of CCF and UHC, the Board may agree to permit another federally sanctioned IRB to act as the IRB of record for Cancer Research studies to be conducted by, or with the assistance of Case, CCF, and/or UHC personnel, at the facilities of such other institution. The Board may agree to function as the IRB of record for another investigator and/or institution if the Cancer Research project involves material collaboration from Case, CCF, and/or UHC. Such agreements will require written letters of agreement and may include the completion of a Federalwide Assurance or other appropriate authorization agreements.

Communication with other IRBs/Institutions/Sites

All Board actions, notices, requests, demands, waivers, determinations, and findings shall be made in writing. In addition to any other notices provided herein, all institutions/sites involved in Cancer Research will be informed in writing to the Human Protections Administrator of the institution or site by the Case Cancer IRB and by the investigator of any adverse events or unanticipated problems that occur. The Case Cancer IRB will inform such persons at all institutions/sites of all full Board actions that the Board may take in response to either a reported event or other protocol specific concern. Notice to an institution or site shall not be imputed or otherwise deemed to occur for any purpose from participation or attendance by an employee, medical staff member, or other person at a Case Cancer IRB meeting.

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Organization and Membership of the Board

Qualification and Selection of Members

The membership of the Board will include individuals with varying backgrounds. The Board shall possess appropriate professional competence to review the diverse types of protocols that are received. The Case Cancer IRB will be able to ascertain the acceptability of the Cancer Research in terms of institutional commitments and policies, all applicable laws and regulations, GCP, JACHO and other standards for professional conduct and practice.

The Board will include at least one member at every meeting who has no current or former employment or other affiliation to Case, CCF, or UHC (and no immediate family member with an affiliation to any of the institutions) other than his/her Case Cancer IRB membership. There will be one member at every meeting whose interests and background are non-scientific (lay person). One Case Cancer IRB member may fulfill both criteria for unaffiliated and lay membership. In addition, the Board that reviews FDA-regulated products (drugs, biologics, and devices) will have at least one member present who is a physician. A prisoner advocate may be called upon to attend a meeting when a study involving prisoners is scheduled.

Membership is selected to assure appropriate diversity, including representation by multiple professions, multiple ethnic backgrounds, both genders, and to include both scientific and non-scientific members in compliance with the law (45 CFR 46.107 and 21 CFR 56.109). Best efforts will be made to achieve Board membership parity among the participating clinical institutions. Board membership will also include, and each meeting shall include, at least one person from each institution. All such members shall serve the Case Cancer IRB and none shall be deemed to be acting in any way as medical staff members, employees, or agents of any individual institution in connection with any of their conduct or duties relating in any way to the Case Cancer IRB.

A licensed attorney for Case, CCF and UHC each may attend IRB meetings but shall not be considered to be Case Cancer IRB members.

Alternate Members

Alternate members may exist for members of the Board. The guidelines presented above will also pertain to the alternates who must have like qualifications to the members for whom they are the alternates.

Management of the Board

Chairperson

Selection and Appointment

The Dean of the Case Western Reserve University Medical School in consultation with the Provost and Chief Academic Officer of CCF and the President of UHC appoints the Board Chairperson, who shall be a member of the Case Cancer IRB. Only Case Western Reserve University faculty with sufficient expertise and experience will be considered for this Case Cancer IRB position and the position shall alternate biennially between CCF and UHC medical staff who are members of the Case IRB.

Length of Term/Service

The Board Chairperson will serve a two-year renewable term. The Dean, considering input from CCF, UHC, Board members, Cancer Investigators, and other Human Protections Administrators, will evaluate the Chair formally on an annual basis.

Duties

The Board Chairperson has the responsibility to ensure the compliance of the Board with all federal, state, and local laws and regulations. The Board Chairperson manages the Board and the matters brought before it according to these Procedures, FDA, DHHS and other applicable laws and regulations pertaining to the rights and welfare of research subjects. The Board Chairperson is responsible for conducting the Board's meetings. The Board Chairperson shall name one vice chair. The vice chair shall be from the other clinical institution and will serve in the Chair's absence.

Removal

After consultation with those involved in the selection of the Chairpersons, the Dean of the Case Western Reserve University Medical School may remove a Chairperson. The Dean shall promptly appoint a qualified replacement from the same institution as the removed chairperson for the remainder of the term (the "Replacement Principle").

Case Cancer IRB Members

Selection and Appointment

Subject to the requirements set forth above, Board members shall be appointed by the Dean of Case School of Medicine in consultation with the Chairperson of the Board.

Length of Term/Service

Members serve a two-year renewable term.

Duties

Members independently evaluate Cancer Research projects involving human subjects that are submitted by Cancer Investigators prior to the Case Cancer IRB meeting, participate in appropriate discussions, and vote to approve, disapprove, require modifications, or table each submission during the Case Cancer IRB meeting in accordance with applicable laws. These actions apply to: (a) initial reviews, (b) continuing reviews, (c) amendments, (d) unanticipated or serious adverse events or problems, (e) change in research scope and (f) advertisements for recruitment of Cancer Research subjects. Members may also review and vote on other pertinent business that the Chairperson includes on the agenda. Experienced members may be appointed by the Chair to review Cancer Research activities that qualify for expedited review. All members, staff and other Cancer IRB persons shall keep all such information concerning the Case Cancer IRB and/or protocols submitted to it, confidential and not use or disclose any information except for lawful Case Cancer IRB purposes. All members, staff and other Cancer IRB persons shall sign a Confidentiality Agreement, agreeing to keep all such information confidential.

Attendance Requirements

Members are required to attend all meetings of the Board. Three consecutive absences by the member may result in removal from the Board.

Removal or Resignation

Members may be removed by the Chairperson in consultation with the Dean or his designee. Any notifications must be submitted in writing to the member and to the Human Protections Administrator of the CCF and UHC IRBs. Qualified replacements shall be promptly appointed in accordance with the Replacement Principle.

Training of IRB Chairs and Members

Orientation

All Case Cancer IRB Chairpersons, members and alternates must complete a core educational program prior to serving on the Case Cancer IRB. The core training track consists of training in Federal Regulations and Board Procedures. Regulatory training provides the basic foundation for protecting human subjects in research, and includes FDA Regulations, HHS Regulations, the differences between them, the historical background to the Federal Regulations, and the Belmont Report.

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Board operation training focuses on the Case Cancer IRB policies and procedures and builds upon the content of the regulatory training by reinforcing the regulations as applied to the policy and procedures of the Case Cancer IRB. Both regulatory and operational training must be completed prior to serving on the Case Cancer IRB.

All board members will be given the opportunity to become familiar with the standard operating procedures of the IRBs of Case, CCF and UHC.

Orientation of New Members

In addition to core training, new members will be assigned to a mentor who is an experienced IRB member and will attend meetings as an observer prior to becoming a voting member. Each new member will be given a Reference Manual containing the FDA (21 CFR Parts 50 & 56), DHHS (45 CFR Part 46), ICH Guidance E6 on GCP, FDA Information Sheets, OHRP's IRB Guidebook, the Standard Operating Procedures of the Case Western Reserve University Case Cancer IRB, Case Western Reserve University's Federalwide Assurance and Case Cancer IRB roster and meeting dates. All of which, as amended, are incorporated herein by reference.

Continuing Education

Board training seminars will be held periodically (at least once a year).

Continuing education information will be distributed and/or posted to the Case website on an ongoing basis to keep the Board informed of issues and debates in the field of human subject protection.

Case IRB members are encouraged to attend national meetings on protection of human subjects.

Reference Materials

A library of books, periodicals, videocassettes and training materials from conferences is maintained for use by Board Members, and the faculty, staff, students, and other employees of the institutions.

Liability Coverage for Case Cancer IRB Members

Case Cancer IRB members, chairs, consultants acting in good faith on behalf of the Board, will be defended and indemnified for any claim of liability under the applicable Case Western Reserve University liability protection or insurance policy, which protects individuals serving on all University committees. Case warrants that it shall maintain for Case Cancer IRB members, chairs, and consultants, at its expense, general, professional and other property and liability insurance coverage for claims or losses caused or alleged to have been caused by or resulting from any act or omission of the Case Cancer IRB or Case Cancer IRB members.

Use of Consultants

The Board may, at its discretion, invite individuals with competence in special areas to assist in the review of complex issues that require expertise beyond or in addition to that available on the Board. These individuals may not vote with the Board (HHS 45 CFR 46.107(f); FDA 21 CFR 56.107(f); ICH 3.2.6).

Cancer Center IRB Office

Support

The Dean of the School of Medicine through the Associate Dean for Research Administration will provide sufficient secretarial/administrative support and adequate resources to ensure all federal, state and Institutional regulations are followed in the timely conduct of IRB matters. The commitment of staff for the IRB is evaluated on a continual basis and additional help will be provided as needed. A Human Protections Administrator will be assigned to the Board.

Adequate meeting and office space shall be provided for the Case IRB and staff. Office equipment and supplies, including file cabinets, computers with internet access and copy machines, shall be made available to the Case IRB and staff.

Duties

The Case Cancer IRB administrator(s) shall prepare meeting agendas, maintain minutes of each Case Cancer IRB meeting, store records according to federal regulations, as well as Case Cancer IRB policy and applicable research grants and agreements. Copies of the agenda, protocols, full grant applications (as applicable) or sponsor research protocols, consent forms, investigator credentials and subject recruitment materials shall be provided to Case Cancer Board members and alternates (as appropriate) in advance of a meeting. Staff shall collect these documents at the end of the meeting; provided that the Human Protections Administrators of CCF and UHC and Cancer IRB members appointed to follow-up on Board issues shall be entitled to receive and retain a complete copy of all materials. Cancer IRB staff shall prepare, store and maintain files required by federal regulation as well as these Procedures. All staff and members shall fully cooperate with any independent audit, or provide a copy of all materials reasonably requested, by CCF and/or UHC.

Training

The Case Cancer IRB Staff will complete the same core educational program provided to Board members. This includes training on applicable federal, state and local regulations and the Case Cancer IRB policies and procedures. The Case Cancer IRB staff will also be provided ongoing and continuing education opportunities (IRB seminars and

workshops; distribution of continuing education information; and access to the Case Cancer IRB website and library).

Member Conflict of Interest

Neither the sponsor, nor the investigator, nor any individual involved in the conduct or oversight of the research activity under review will participate in the Board review or conclusions except to provide information. No person may participate in the Board's initial or continuing or other review or oversight of any project in which the person has a conflicting interest, except to provide information requested by the Board.

For purposes of these Procedures, a "conflict of interest" may be defined as follows:

1. In situations as such under applicable law or policy or in which a Case Cancer IRB member, sponsor, investigator, individual, family member or institution has or appears to have an opportunity to influence Case Cancer IRB action or to use Case Cancer IRB resources or confidential information in any way that could lead to professional, personal, economic or other gain, or to otherwise give rise to an improper advantage or to adversely affect the rights or welfare of Human Subjects, or the complete unbiased review or conduct of the research or integrity of analysis or reporting of results;
2. A member who also serves as a Principal Investigator on a project receiving Board review; or who has enrolling authority for any already identified patient that they reasonably expect to enroll in the protocol under consideration;
3. A member who has a primary role in the oversight, design or conduct of the project or has a role in the analysis or management of the clinical trial data;
4. A member who is also serving as a Chair of the Case Comprehensive Cancer Center Data Safety and Monitoring Committee, or members who sit on study committees or data monitoring boards for protocol from which they may be involved;
5. A member who has proprietary interest in the research, such as a licensing agreement, copyright, patent or trademark; and
6. A member within two years before deliberations receives any compensation from any enterprise involved in the protocol under consideration;

Members having a conflict of interest shall disclose the conflict and recuse themselves from participation during review of that research project except to provide information to the Board on request. Persons identified in this section shall leave the meeting during the discussion and the vote on any motion to approve or disapprove the research in question. When a person with a conflict of interest leaves the room he/she cannot be counted towards a quorum. If at any time during a given meeting for which a quorum initially existed there is no longer at least one faculty or medical staff member or employee of Case, CCF and/or UHC the quorum for the meeting shall be broken and the Board shall not take any further action. The Board minutes will reflect defined conflicts in addition to potentially enrolling authority conflicts for Board members existing for each protocol reviewed. (HHS 45 CFR 46.107(e); FDA 21 CFR 56.107(e); ICH 3.2.3)

Investigator Conflict of Interest

The Case Cancer IRB is responsible for reviewing possible investigator and institutional conflicts of interest as they relate to the protection of Human Subjects. Any such conflicts shall be disclosed to potential subjects in the informed consent document approved by the Board, as they may affect subjects' decisions to participate in the research.

In the protocol application, investigators will be asked if anyone participating in the study has a significant financial or other interest in any organization that might reasonably appear to affect or affect the outcome of the research. A "significant financial interest" exists if salary or other compensation is expected to exceed \$10,000 or more in the next twelve months, or represents an equity interest with a fair market value of more than \$10,000 or 5% or more ownership interest (total ownership interest of the faculty member, spouse or significant other, and dependent children) or intellectual property rights. If a significant financial interest is disclosed, investigators or key personnel will then be asked if the interest was reported on his/her most recent conflict of interest disclosure form (if it has not, the IRB office can direct investigators to the form). The Case Conflict of Interest Committee will formulate a plan to reduce, manage, or eliminate the conflict. The Board shall not approve any research if a disclosure form has not been completed and received by Case Conflict of Interest Committee or if a response to a request for additional information by a Case Cancer IRB member is not received to the satisfaction of the member making such request before a vote. The Board may approve a more stringent plan to manage the conflict but may not adopt a more lenient plan and shall provide written notice to the Human Protections Administrator of the CCF and UHC IRBs disclosing the conflict and any approved management plan with the notice approving the research. Additionally, investigators shall disclose the financial interest in the informed consent document.

For the general Case Western Reserve Individual Conflict of Interest Policy and Procedures, please see the Following:

http://ora.ra.cwru.edu/COI%20General%20Policy%20Revised%20_08-01_.pdf

Institutions shall report to the Cancer IRB, as appropriate, on relevant institutional conflicts of interest.

Functions of the Board

Materials distributed prior to Board Review

Board members will be given the Cancer Research IRB application, protocol, consent, recruitment and conflict of interest materials in advance of the Board meeting. The primary reviewer will receive the same materials with the addition of any investigational drug information and experience to date. All Board members will also receive the minutes of the meeting of Case Cancer Center's Protocol Review and Monitoring Committee, when applicable, which can be used to determine scientific merit. If the protocol is under consideration for continuing review, each member will receive the continuing review application and any summaries of study activity that have been received by the IRB office.

Case IRB staff in consultation with the Chairperson shall determine if an Investigational New Drug Exemption (IND) or Investigational Device Exemption (IDE) is needed before review can take place and shall ensure that any necessary IND or IDE is obtained from the FDA by the Board before any research activity is commenced at any institution.

Conducting Initial Review

The Board shall follow DHHS and FDA regulations and, when applicable, ICH guidance, concerning IRBs and the requirements of these Procedures for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator, and when applicable, to the Human Protections Administrator of Case, CCF and UHC IRBs. (HHS 45 CFR 46.108; 46.103(b) (4); 46.103(b) (5); FDA 21 CFR 56.108 (a) (1); ICH 3.3)

The Board must ensure that the following requirements are satisfied before it approves research:

1) Risks to subjects are minimized by:

- using procedures which are consistent with sound research design; and
- which do not unnecessarily expose subjects to risk; and
- Whenever appropriate, using procedures already being performed on the subjects for diagnostic or treatment purposes (HHS 45 CFR 46.111(a) (1); FDA 21 CFR 56.111(a) (1)).
- Risks to subjects are reasonable in relationship to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

In evaluating risks and benefits, the Board should consider only those risks and benefits that may result from the research as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research. The Board should not consider possible long-range effects of applying knowledge gained in the research (e.g. the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility (HHS 45 CFR 46.111(a)(2); FDA 21 CFR 56.111(a)(2); ICH 2.2).

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- 2) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which the research will be conducted.
- 3) Determine that informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with HHS 45 CFR 46.116, FDA 21 CFR Part 50, and as outlined in these Procedures (HHS 45 CFR 46.111(a)(4); FDA 21 CFR 56.111(a)(4); ICH 2.9).
- 4) Determine that informed consent will be appropriately documented in accordance with and to the extent required by HHS 45 CFR 46.117 and FDA 21 CFR 50.27.
- 5) Determine that there are adequate provisions in the research plan, where appropriate, for monitoring the data collected to ensure the safety of subjects (HHS 45 CFR 46.111(a) (6); FDA 21 CFR 56.111(a) (6)).
- 6) Determine that there are adequate provisions to protect privacy of subjects and to maintain the confidentiality of data, where appropriate (HHS 45 CFR 46.111(a) (7); FDA 21 CFR 56.111(a) (7); ICH 2.11).
- 7) Determine that plans for subject recruitment that involve advertising or other direct contact with potential subjects outside the doctor-patient relationship are consistent with the protocol, the consent form, applicable law and FDA Guidelines found in the FDA Information Sheets.
- 8) Determine that there are appropriate additional safeguards included in the study to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence e.g., children, prisoners, pregnant women, handicapped or mentally disabled persons, persons with acute or severe physical or mental illness, persons who are economically or educationally disadvantaged, or persons who are vulnerable because they are institutionalized (HHS 45 CFR 46.111(b); FDA 21 CFR 56.111(b)).

Informed Consent

The Board shall ensure that information given to subjects as part of informed consent is in accordance with HHS 45 CFR 46.116; ICH 4.8 and FDA 21 CFR 50.25 and other applicable law.

The Board shall require that information, in addition to that required by regulations, be given to subjects when in the Board's judgment the information would meaningfully add to the protection of the rights and welfare of subjects (HHS 45 CFR 46.109(b); FDA 21 CFR 56.109(b); ICH 3.1.5)).

The Board has authority to observe or have a third party observe the consent process and the

research (HHS 45 CFR 46.109 (e); FDA 21 CFR 56.109(f); ICH 5.15.1). The chair may designate a third party to conduct a site visit to review the informed consent process at anytime.

The Board shall ensure that informed consent is documented in accordance with and to the extent required by HHS 45 CFR 46.116, FDA 21 CFR 50.27, and ICH 4.8, unless documentation is waived by the Board as provided in HHS 45 CFR 46.109(c) and 46.117, and in FDA 21 CFR 56.109(c).

Consent Form Requirements

1. The consent form must be:
 - approved by the Board;
 - marked with an approval stamp with expiration date stamped on the consent;
 - signed by the subject or the subject's legally authorized representative (HHS 45 CFR 46.117 (a)); FDA 21 CFR 50.27 (a); ICH 4.8.8);
 - signed by the person who conducted the informed consent discussion (ICH 4.8.8); and
 - a signed and dated copy must be given to the subject or the subject's legally acceptable representative signing the form (HHS 45 CFR 46.117(a)); FDA 21 CFR 50.27(a); ICH 4.8.11).

2. The consent form must be either:
 - A written consent document that embodies the elements of informed consent required by HHS 45 CFR 46.116 and 46.117(b)(1); or
 - A short form written consent document stating that the elements of information consent required by 45 CFR 46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation, and the IRB will review and approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative, the witness, person obtaining consent and the investigator. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall also sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form. (45 CFR 46.117(b(2)); FDA 21 CFR 50.25 and 50.27(b); ICH 4.8)

3. Elements of Consent

Informed consent shall include the following elements:

- A statement that the study involves research; (HHS 45 CFR 46.116(a) (1); FDA 21 CFR 50.23(a) (1); ICH 4.8.10(a));
- An explanation of the purposes of the research (HHS 45 CFR 46.116(a) (1); FDA 21 CFR 50.23(a) (1); ICH 4.8.10(b));
- The expected duration of the subject's participation in the research (HHS 45 CFR 46.116(a) (1); FDA 21 CFR 50.23(a) (1); ICH 4.8.10(s));
- A description of the procedures to be followed (HHS 45 CFR 46.116(a) (1); FDA 21 CFR 50.23(a) (1); ICH 4.8.10(d));
- Identification of any procedures which are experimental (HHS 45 CFR 46.116(a)(1); FDA 21 CFR 50.25(a)(1); ICH 4.8.10(f));
- A description of any reasonably foreseeable risks or discomforts to the subject (HHS 45 CFR 46.116(a)(2); FDA 21 CFR 50.25(a)(2); ICH 4.8.10(g));
- A description of any benefits to the subject or to others which may reasonably be expected from the research (HHS 45 CFR 46.116(a)(3); FDA 21 CFR 50.25(a)(3); ICH 4.8.10(h));
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject (HHS 45 CFR 46.116(a)(4); FDA 21 CFR 50.25(a)(4); ICH 4.8.10(i));
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, and a statement of the possibility that the Food & Drug Administration may inspect the records (HHS 45 CFR 46.116(a)(5); FDA 21 CFR 50.25(a)(5); ICH 4.8.10(n) and (o));
- For research involving more than minimal risk, an explanation as to whether any compensation is available if injury occurs; and whether any medical treatments are available if injury occurs; and if so, what they consist of, or where further information can be obtained (HHS 45 CFR 46.116(a)(6); FDA 21 CFR 50.25(a)(6); ICH 4.8.10(j));

- An explanation of whom to contact for answers to pertinent questions about the research, and research subject's rights; and whom to contact in the event of a research related injury to the subject (HHS 45 CFR 46.116(a)(7); FDA 21 CFR 50.25(a)(7); ICH 4.8.10(q)); and
- A statement that participation is voluntary, that refusal to participate involves no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled (HHS 45 CFR 46.116(a) (8); FDA 21 CFR 50.25(a) (8); ICH 4.8.10(m)).

When applicable, one or more of the following elements of information shall also be provided to each subject:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable (HHS 45 CFR 46.116(b)(1); FDA 21 CFR 50.25(b)(1));
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent (HHS 45 CFR 46.116(b)(2); FDA 21 CFR 50.25(b)(2); ICH 4.8.10(r));
- Any additional costs to the subject that may result from participation in the research (HHS 45 CFR 46.116(b)(3); FDA 21 CFR 50.25(b)(3); ICH 4.8.10(l));
- The consequence(s) of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject (HHS 45 CFR 46.116(b)(4); FDA 21 CFR 50.25(b)(4));
- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue will be provided to the subject (HHS 45 CFR 46.116(b)(5); FDA 21 CFR 50.25(b)(5); ICH 4.8.10(p));
- The approximate number of subjects involved in the study (HHS 45 CFR 46.116(b)(6); FDA 21 CFR 50.25(b)(6); ICH 4.8.10(t)); and
- The trial treatment(s) and the probability of random assignment to placebo or to each treatment (ICH 4.8.10(c)).

The Board may require that information in addition to that required in Federal Regulations (HHS 45 CFR Part 46); FDA 21 CFR Part 50) and ICH 4.8 be given

to research subjects when in its judgment the information would meaningfully add to the protection of the rights and welfare of subjects (HHS 45 CFR 109(b); FDA 21 CFR 56.109(b); ICH 3.1.5).

Documentation of Consent

The Board, for some or all subjects, may waive the requirement that the subject or the subject's representative sign a written consent document if it finds that:

- the research presents no more than minimal risk of harm to patients; and
- the research involves no procedures for which written consent is normally required outside the research context (HHS 46 CFR 45.117(c)(2); FDA 21 CFR 56.109(c)).

If the Board waives the requirement of documentation of informed consent as identified above, it may require the investigator to provide subjects with a written statement regarding the research (HHS 45 CFR 46.117(c)(2); FDA 21 CFR 56.109(c)).

For research under NIH jurisdiction, but not FDA jurisdiction, the Board may also waive the requirement for a signed written consent document if the only link between the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (HHS 45 CFR 46.117(c)(1)).

Waiver of Consent

The Board may waive the requirement for informed consent per 45 CFR 46.116 (d) (or allow an alteration of some or all of the elements of informed consent) only if the Board finds that expressly in writing and documents that each of the following four elements is met. This is different than waiving the requirement of documentation of informed consent, as identified directly above in these Procedures.

- the research involves no more than minimal risk to the subjects; and
- the waiver or alteration will not adversely affect the rights and welfare of the subjects; and
- the research could not practicably be carried out without the waiver or alteration; and
- whenever appropriate, the subjects will be provided with additional pertinent information after participation (45 CFR 46.116(d)).

If the research involves FDA regulated article under 21 CFR Parts 50 and 56, the Board may waive the requirement for prior consent only if the research involves the individual

emergency use of a test article, as provided for in FDA 21 CFR 50.23 (a)-(c), 56.104(c), and 56.102(d) and these Written Procedures (if such emergency use is reported to the Board after the waiver has already occurred, the Board will acknowledge rather than approve the waiver).

The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided below), both the investigator and another qualified physician on the medical staff of the institution at which the clinical research activity is conducted who is not otherwise participating in the clinical investigation certify in writing all of the following:

- The human subject is confronted by a life-threatening situation necessitating the use of the test article;
- Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject;
- Time is not sufficient to obtain consent from the subject's legal representative; and
- There is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in the above paragraph of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by another qualified physician on the medical staff of the institution at which the clinical research activity is conducted who is not participating in the clinical investigation.

The documentation required in this section shall be submitted to the IRB within 5 working days after the use of the test article.

Illiterate Subjects

Illiterate persons may have informed consent or permission information read to them and may "make their mark" in a manner consistent with the laws of the State of Ohio in which the research is conducted to document their understanding. In this situation, it is also desirable to obtain the signature of an impartial witness to the process and the signature of the person conducting the consent or permission interview.

Non-English Speaking Subjects

When a full-length consent form embodying all required elements is required by the Cancer IRB to document consent, that form must be written in a language understandable to the subject. The Board shall require that appropriately translated consent documents be submitted to the Case Cancer IRB for review and approval prior to their use in enrolling subjects.

When a short-form consent document is used, the short form itself must be written in a language understandable to the subject.

In all cases, there must be a member of the research staff who can speak and read the language of the potential subject. The use of translators is not permitted due to the confidential nature of the information disclosed and the complexity of the subject's medical condition.

Emergency Research Consent Waiver

The Board may waive the requirement for informed consent for research involving emergency medical situations if it finds and documents that the requirements of 21 CFR 50.24 are met.

In order to approve an emergency research consent waiver study, the Board shall find and document all of the following:

The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

Obtaining informed consent is not feasible because:

- Subjects will not be able to give informed consent because of their medical condition;
- The intervention under investigation must be administered before consent from the subject's legally authorized representative is feasible; and
- There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

Participation in the Cancer Research holds out the prospect of direct benefit to the subjects because:

- Subjects are facing a life-threatening situation that necessitates intervention;
- Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence supports the potential for the intervention to provide a direct benefit to the individual subjects; and

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- Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

The clinical investigation could not practicably be carried out without the waiver.

The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative for consent within that window rather than proceeding without consent. The investigator will summarize the efforts made to contact legally authorized representatives and make this information available to the Board at the time of continuing review.

The Board has reviewed and approved informed consent procedures and an informed consent document consistent with 45 CFR 46.116 and 21 CFR 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The Board has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation

Additional protections of the rights and welfare of the subjects will be provided, including, at least:

- Consultation (including, where appropriate, consultation carried out by The Board) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn.
- Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits.
- Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results.
- Establishment of an independent data-monitoring committee to exercise oversight of the clinical investigation.
- If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window, a family member of the subject who is not a legally authorized representative, and asking whether he or she objects to the subject's

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participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the Board at the time of continuing review.

The Board will ensure that there are procedures in place to inform at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The Board shall also ensure that there are procedures in place to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is informed about the clinical investigation, and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

The Board shall require that a separate Investigational New Drug Exemption (IND) or Investigational Device Exemption (IDE) will be obtained by the sponsor, even for marketed products.

The Board shall promptly notify in writing the investigator and sponsor when it determines that it cannot approve an emergency consent exception study. The notice shall include the reasons for the disapproval.

The Board may require additional protections for subjects in an emergency Cancer Research consent waiver study as appropriate and shall, in all such cases, notify the Human Protection Administrators of the IRB of CCF and UHC, as appropriate.

Cancer Research Involving Children

When the Board reviews Cancer Research involving children, the Board will determine which of the four following risk/benefit categories the research fits into. The Board's designation will be entered into the minutes for that meeting. The four possible categories are:

Category 1 (45 CFR 46.404; 21 CFR 50.51) - Research not involving greater than 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.

Examples of minimal risk include:

- studies involving only the collection of blood samples by stick or venipuncture, not to exceed 550 ml in an 8 week period for adults, or for children the lesser of 50 ml or 3 ml per kg in an 8 week period;
- studies involving the collection of biological specimens by non-invasive means;
- studies involving the collection of data through noninvasive procedures routinely employed in clinical practice, such as electrocardiography and ultrasound; and
- studies consisting only of questionnaires that do not contain emotionally disturbing questions.

Category 2 (45 CFR 46.405; 21 CFR 50.52) –Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

For category 2 research to be approved, the Board must find that:

- the risk is justified by the anticipated benefits to the subjects, and
- the relation of the anticipated benefit to the risk must be at least as favorable to the subjects as that presented by available alternative approaches

Category 3 (45 CFR 46.406; 21 CFR 50.53) –Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

For category 3 research to be approved, the Board must find that it meets the following requirements:

Nontherapeutic research may be conducted in children with the consent of a legally authorized representative provided the following conditions are met:

- The risk represents a minor increase over minimal risk;

- 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;
- The intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition;
- Adequate provisions are made for soliciting and documenting assent of the children; and
- Adequate provisions are made for soliciting the permission of both parents of each child unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. (45 CFR 46.407 and 408).

Category 4 (45 CFR 46.407; 21 CFR 50.54) –Research not fitting into categories 1 through 3, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Category 4 research under NIH jurisdiction cannot be performed without review by the Secretary of the Department of Health and Human Services as outlined in 45 CFR 46.407.

Category 4 research under FDA jurisdiction cannot be performed without review by the Commissioner of Food and Drugs as outlined in 21 CFR 50.54.

Assent Determination

After the Board makes the risk/benefit determination, they must consider the issue of child assent, as described in 45 CFR Part D, 46.408(a) or 21 CFR 50.55, as applicable. The Board must decide whether assent is necessary, and also whether and how it will be documented if it is necessary.

Among the assent possibilities the Board can consider are the following:

- No assent;
- Verbal assent, without documentation;
- Verbal assent, with documentation by the investigator and/or the legally authorized representative(s);
- Written assent form, with subject signature; or
- Subject signature block on consent form (for older children only).

Minor subjects 6 years of age or over should be involved in the decision to participate in a research project. Minor subjects 12 years of age and older may sign an assent after the parent or legal guardian has given consent unless:

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- The research holds out the prospect of direct benefit to the subject and which is available only in the context of the research (e.g., new therapy when none is available).
- The subject is incapable, mentally or emotionally, of being reasonably consulted.
- The Case Cancer IRB specifically waives the requirement.
- Except when the above exclusions are present, children between the ages of six and twelve must give positive assent directly or through their parents to participation in the research.

Cancer Research Involving Pregnant Women and Fetuses
(45 CFR 46, Subpart B)

1. When the Board considers Cancer Research involving pregnant women and fetuses, it shall ensure that:
 - 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;
 - The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
 - Any risk is the least possible for achieving the objectives of the research;
 - If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of 45 CFR 46 subpart A;
 - If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of 45 CFR 46 subpart A, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
 - Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
 - For children who are pregnant, assent and permission are obtained in accord with the provisions of 45 CFR 46 subpart D and/or 21 CFR 50, subpart D;
 - No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
 - Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

- Individuals engaged in the research will have no part in determining the viability of a neonate.

When the Board considers Cancer Research involving neonates, it shall ensure that:

Neonates of uncertain viability may be involved in Cancer Research if all of the following conditions are met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2. Individuals engaged in the research will have no part in determining the viability of a neonate.
3. The Case Cancer IRB determines that:
 - The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
 - The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
 - The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

Nonviable neonates may not be involved in Cancer Research unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

5. The legally effective informed consent of both parents of the neonate is obtained in accord with 45 CFR 46, subpart A, except that the waiver and alteration provisions of 45 CFR Sec. 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in Cancer Research only to the extent permitted by and in accord with the requirements of 45 CFR 46 subparts A and D.

The Board may consider approval of HHS-funded Cancer Research not otherwise approvable under this Procedure which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates if:

The Secretary of HHS, after consultation with a Board of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either: (1) That the research in fact satisfies the conditions of Sec. 46.204, as applicable; or (2) The following:

- The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
- The research will be conducted in accord with sound ethical principles; and
- Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

Cancer Research Involving Prisoners (45 CFR 46, Subpart C)

The purpose of this section is to set out the additional safeguards for the protection of prisoners involved in Cancer Research. Prisoners may be under constraints because of their incarceration, which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research.

Prisoner means 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.

The Board, when reviewing Cancer Research involving prisoners, will have at least one prisoner representative, a member who is or was a prisoner or who has the appropriate background and experience to represent the rights and welfare of the prisoners. When a convened Board reviews research involving prisoners, the prisoner representative will be present at the meeting.

In addition to its other responsibilities prescribed in these Written Procedures, the Board shall review research involving prisoners only if it finds that:

- The research under review represents one of the categories of the research permissible under 46.306(a)(2);
- 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;
- The risks involved in the research are commensurate with the risks that would be accepted by non-prisoner volunteers;
- 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 particular research project;

- The information is presented in language which is understandable to the subject populations;
- Adequate assurance exists that parole Board will not take into account 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
- Where the Board 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, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Biomedical or behavioral research may involve prisoners as subjects only if the Board has approved the research considering the above requirements and the proposed research involves solely the following:

- 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;
- 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;
- 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; or
- 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 studies require the assignment of prisoners to control groups which may not benefit from the research, the study may proceed only after the Board Chair has consulted with appropriate experts, including experts in penology medicine and ethics, and published notice in the Federal Register, of his/her intent to approve such research.

Cancer Research Involving Other Vulnerable Adults

When all or some of the subjects in proposed Cancer Research are vulnerable adults, the Board will ensure the review of the research is in compliance with ICH Guidelines and applicable laws.

When the Board designates the subjects in a research protocol as being vulnerable adults, the Board will determine which of the four following risk/benefit categories the research fits into:

1. Category 1—Research not involving greater than 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.

2. Category 2—Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

For Category 2 research, the Board will ensure that the research meets the requirements for conducting initial review as described in these written procedures, and will involve additional safeguards as appropriate.

3. Category 3—Research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects. If any or all of the adult subjects in Category 3 research are incompetent, the ICH requires the following additional findings by the IRB:

Non-therapeutic research may be conducted on a legally incompetent subject with the consent of a legally acceptable representative provided the following five conditions are met:

- a. The objectives of the study cannot be met by means of a study in subjects who can give informed consent personally.
- b. The foreseeable risks to the subjects are low.
- c. The negative impact on the subject's well-being is minimized and low.
- d. The study is not prohibited by law.
- e. The written approval of the Board specifically address the inclusion of subjects with a legally authorized representative.

4. Category 4—Research not fitting into categories 1 through 3.

If any or all of the adult subjects in Category 4 research are incompetent, the ICH requires the following additional findings by the Case Cancer IRB:

Non-therapeutic research may be conducted on a legally incompetent subject with the consent of a legally acceptable representative provided the following five conditions are met:

- The objectives of the study cannot be met by means of a study in subjects who can give informed consent personally.
- The foreseeable risks to the subjects are low.
- The negative impact on the subject's well-being is minimized and low.
- The study is not prohibited by law.
- The written approval of the Case Cancer IRB specifically addresses the inclusion of subjects with a legally authorized representative.

The Board will consider additional safeguards for the research subjects on a case-by-case basis (FDA 21 CFR 56.111(b); HHS 45 CFR 46.111(b)).

For studies involving the possibility of consent by legally authorized representatives for adult subjects, the Board must consider the issue of subject assent. The Board must determine whether assent is necessary, and how it will be documented if it is necessary (ICH 4.8.12).

Review of Devices

Review of Cancer Research involving medical devices

Before reviewing Cancer Research involving a medical device for human use, the Board will determine if the device is a Significant Risk (SR) Device, a Non-Significant Risk (NSR) Device, or whether the research use of the device is exempt from the IDE regulations.

- If the Board determines that the device is NSR, this finding will be included in the minutes, and the Board may proceed to review the research activities and investigator under its normal procedures for reviewing research projects.
- If the FDA has issued an Investigational Device Exemption (IDE) for the proposed use of the device, then it is automatically an SR device. This finding will be noted in the minutes.
- If FDA has not issued an IDE for the proposed use of the device, then the Board shall consider the following elements in determining if the device is SR:
 - An explanation provided by the sponsor of why the device is not a significant risk device, and
 - Whether the use of the device might cause harm to any of the subjects, and the nature of the harm that may result from use of the device.

Note: If the subject must undergo a medical procedure as a part of the study, and that medical procedure is not one which the subject would otherwise undergo as part of standard medical care, the Board must consider the risks associated with the procedure as well as the use of the device. If potential harm to subjects could be life-threatening, could result in permanent impairment of body function, or permanent damage to body structure, the device should be considered SR.

- If the Board determines the device is SR, and there is no IDE assigned, it will provide the investigator and, if appropriate, the sponsor, with its finding. The sponsor is responsible for notifying the FDA of the Board's SR determination. The Board will not review the research until the sponsor provides proof that the FDA has granted an IDE to the sponsor. If the FDA has not responded to the IDE application, as described in FDA 21 CFR 812.30, this proof, required above, may consist of a letter showing that an IDE application was submitted at least 30 days prior to the date on which the Board reviews the research.
- If the Board determines that the investigation meets one of the IDE exemptions listed at 21 CFR 812.2(c), this finding will be noted in the minutes, and the Board will not make an SR/NSR determination. Also, if the investigation involves a device that is cleared for marketing through the PMA process, and the device is being studied for the purpose(s) for which the device is labeled, the Board will consider the investigation exempt from the

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IDE regulations. This finding will be noted in the minutes, and the Board will not make an SR/NSR determination.

Cancer Research involving a medical device for human use that qualifies as a Non-Significant Risk (NSR) Device (unless the device is banned), may begin upon approval by the Case Cancer IRB and does not require the issuance of an Investigational Device Exemption (IDE) by the FDA (FDA 21 CFR 812.2 (b)(1)).

Research involving a medical device for human use that does not qualify as NSR device is classified as a Significant Risk (SR) Device. Cancer Research involving SR devices (unless the device is banned) cannot begin until the FDA issues an IDE and approval is granted by the Case Cancer IRB (FDA 21 CFR 812.30 (a)).

A significant risk device means an investigational device that meets any of the following criteria (FDA 21 CFR 812.3(m)):

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject.
- Is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject.
- Is for a use of substantial importance in diagnosis, 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
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Review of Humanitarian Use Devices (HUD)

Humanitarian Use Devices are intended to benefit subjects in the treatment or diagnosis of diseases or conditions that affect or manifest in fewer than 4000 individuals in the United States per year. Humanitarian Use Devices are considered by the FDA to be approved for marketing.

IRB review of Humanitarian Use Devices is required under Federal Regulation (FDA 21 CFR Part 814). Before reviewing a Humanitarian Use Device, the Board shall:

- Determine that the FDA has granted a Humanitarian Device Exemption (HDE) to the sponsor.
- Determine that the investigator intends to use the Humanitarian Use Device according to its FDA approved use.

After the Board has determined that the FDA has granted an HDE, the Board may proceed to review the Cancer Research activities and investigator under its normal procedures for reviewing Cancer Research projects.

Informed consent is not required for use of a Humanitarian Use Device in accordance with its FDA approved use. However, the Board may require consent in such instances at its discretion. The Board will require informed consent for the **research use** of a Humanitarian Use Device.

Emergency Use of Unapproved Medical Devices

21 CFR 56.104

Definition

Emergency Use: use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

Unapproved Medical Device: a device that is used for a purpose or condition which the device requires, but one which does not have an approved application for premarket approval.

Need for an IDE

An unapproved device may be used in human subjects only if it is approved for clinical testing under an approved application for an Investigational Device Exemption (IDE).

The FDA recognizes that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to FDA that an emergency actually existed.

Requirements for Emergency Use

Each of the following conditions must exist to justify emergency use:

- the patient is in a life-threatening condition that needs immediate treatment;
- no generally acceptable alternative for treating the patient is available; **and**
- because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

The FDA expects the physician to determine whether these criteria have been met, to assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist. The physician may not conclude that an emergency exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. Physicians should be aware that the FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

In the event that a device is to be used in circumstances meeting the above criteria, the device developer should notify the Center for Devices and Radiological Health (CDRH) Program

Operation Staff by phone (301-594-1190) immediately after shipment is made. Nights and weekends, contact the Division of Emergency & Epidemiological Operations (202-857-8400).

Note: An unapproved device may not be shipped in anticipation of an emergency.

The FDA expects the physician to follow as many subject protection procedures as possible, including:

- obtaining an independent assessment by an uninvolved physician;
- obtaining informed consent from the patient or a legal representative;
- notifying institutional officials;
- notifying the Case Cancer IRB; and
- obtaining authorization from the IDE holder, if an approved IDE for the device exists.

Please note that **data from these activities may only be counted toward research to the extent required by FDA regulations.**

After-Use Procedures

After an unapproved device is used in an emergency, the physician should:

- report to the Case Cancer IRB within five working days;
- evaluate the likelihood of a similar need for the device occurring again and, if future use is likely, immediately initiate efforts to obtain Case Cancer IRB approval and an approved IDE for the device's subsequent use; and
- if an IDE for the use does exist, notify the sponsor of the emergency use, or if an IDE does not exist, notify the FDA of the emergency use (CDRH Program Operation Staff at 301-594-1190) and provide the FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results.

Subsequent emergency use of the device may not occur unless the physician or another person obtains approval of an IDE for the device and its use.

Note: If an IDE application for subsequent use has been filed with the FDA and the FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist.

Developers of devices that could be used in emergencies should anticipate the likelihood of emergency use and should obtain an approved IDE for such uses.

Emergency Use of an Investigational Drug or Biologic

21 CFR 56.104, 21 CFR 50.23

Definitions

Emergency Use: use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

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 these sections.

Obtaining an Emergency IND

The emergency use of an unapproved investigational drug or biologic requires an approved application for an Investigational New Drug (IND). If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, the FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means (21 CFR 312.36):

- For **drug products** contact: Document Requirements & Services Branch at 301-827-1501
- For **biologic products** contact: Division of Congressional & Public Affairs at 800-835-4709
- Nights & weekends contact: Division of Emergency & Epidemiological Operations at 202-857-8400

Emergency Exemption from Prospective Case Cancer IRB Approval

The FDA exempts from prospective Case Cancer IRB review the "emergency use" of a test article, provided that such emergency use (as defined above) is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. Please note that **data from these activities may only be counted toward research to the extent required by FDA regulations.**

Exception from Informed Consent Requirement

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and another qualified physician on the medical staff of the institution at which the clinical research activity is conducted who is not otherwise participating in the clinical investigation certify in writing **all** of the following (21 CFR 50.23):

- the human subject is confronted by a life-threatening situation necessitating the use of the test article;
- informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject;
- time is not sufficient to obtain consent from the subject's legal representative;
- there is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination by another qualified physician on the medical staff of the institution at which the clinical research activity is conducted who is not otherwise participating in the clinical investigation in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, shall be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The documentation required of the investigator and the independent physician and described above shall be submitted to the IRB within 5 working days after the use of the test article.

Emergency Medical Care

45 CFR 46.103(b), 45 CFR 46.116(f)

The above cited regulatory provisions have two objectives:

- To make clear that emergency medical care for patients may be provided without regard to Case Cancer IRB review and approval.

- To require Case Cancer IRB review and approval prior to initiation of research involving human subjects.

Confusion can arise when both objectives appear to pertain to the needs of the same person. OHRP has, thus, provided the following clarification:

- Whenever emergency care is initiated without prior Case Cancer IRB review and approval, the patient may not be considered to be a research subject.
- Such emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity.

In other words, HHS regulations for the protection of human subjects do not permit research activities to be started, even in emergency, without prior Case Cancer IRB review and approval.

If the emergency care involves drugs, devices, or biologics that are considered to be investigational by the FDA, then it may be necessary to meet FDA requirements to use the investigational article for emergency purposes.

Conducting Continuing Review

Case Cancer IRB shall conduct continuing review of all approved Cancer Research activities in compliance with applicable laws.

1. Approved projects shall be re-reviewed at intervals appropriate to the degree of risk to which subjects are exposed. In no case will the interval between reviews be longer than one calendar year. Except in cases where the initial review was expedited, continuing review shall be conducted at a convened meeting of the Board (HHS 45 CFR 46.108(b); 46.109(e); FDA 21 CFR 56.108(a)(I); ICH 3.1.4)).
2. Notification that continuing review is to take place will be sent to investigators at least 45 days prior to the continuing review. Investigators will submit appropriate reports to the IRB Office on ongoing Cancer Research activities at least ten days prior to the scheduled continuing review.
3. All changes in approved Cancer Research are to be promptly reported to and approved by the IRB Board (HHS 45 CFR 46.103(b)(4) before being initiated by the investigator (FDA 21 CFR 56.108(a)), except where necessary to eliminate apparent immediate hazards.
4. The Board has authority to suspend or terminate the approval of Cancer Research that is not being conducted in accordance with federal or state regulations or in accordance with stipulations imposed on the Cancer Research activity by the Board. Any suspension or termination will be reported promptly to the investigator by the Chairperson, who will inform the Dean of the Medical School or his designee and the Human Protections Administrator at CCF and UHC in writing. The Human Protections Administrator of the Case Cancer IRB Office will notify the FDA and the Office for Protection from Research Risks of the suspension or termination (HHS 45 CFR 46.108(a);(FDA 21 CFR 56.113).
5. At the time of ongoing review of the project, the Board shall make a determination of whether already enrolled subjects must sign any newly approved consent form or if a new consent form shall be used only by future enrollees in the study.

Adverse Events and Unanticipated Problems

Purpose

The purpose of this policy is to ensure that the reporting and analysis of adverse events and unanticipated problems occur in a timely, meaningful way so that human subjects can be protected from avoidable harms. This policy will outline the procedure to ensure prompt reporting to the Board, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency heads of unanticipated problems involving risks to participants or others.

Due to the number and frequency of events that occur in Cancer research, it is the intention of the Board to focus its review on the reporting of serious adverse events and/or unanticipated problems to ensure the protections of research participants. This will ensure that the Board will provide a meaningful review to ongoing Cancer research.

Definitions:

Adverse event¹: any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research or any risk associated with the research or the research intervention, or the assessment.

Adverse events may be the result of:

- (a) the interventions and interactions used in the research;
- (b) the collection of identifiable private information in the research;
- (c) an underlying disease, disorder, or condition of the subject; and/or
- (d) other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are at least partially the result of (a) or (b) would be considered related to the research, whereas adverse events solely related to (c) or (d) would be considered unrelated to the research.

Expected adverse event: an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

Unexpected adverse event: an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

¹ Appendix A provides additional definitions for adverse event.

External adverse events: adverse events experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the Board has jurisdiction.

Internal adverse events: adverse events experienced by subjects enrolled at the site(s) under the IRB's jurisdiction for either multicenter or single-center research projects. In the case of an internal adverse event the Principal Investigator (PI) typically becomes aware of the adverse event directly from the subject, another collaborating local investigator, or the subject's healthcare provider.

Unanticipated problems: those events that (1) are not expected given the nature of the research procedures and the subject population being studied; and (2) suggest that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized.

Significance of an adverse event is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe or life threatening). According to National Cancer Institute Guidelines, severity can be defined by the following grades of events:

Grade 1 are mild adverse events. (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)

Grade 2 are moderate adverse events (e.g., minimal intervention; local intervention; non-invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grade 3 are severe and undesirable adverse events (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grade 4 are life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

Grade 5 is a fatal adverse event resulting in death. Death which occur after the subject's research participation has ended do not need to be reported to the IRB unless the death is related to study participation.

Serious adverse event: Any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when,

based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. (As defined by FDA regulations at 21 CFR 310.305(b), 312.32(a), and 314.80(a))

Reportable Events

The following four types of events are required to be reported to the Board:

- (1) Adverse events that are serious, unexpected, and related or possibly related to participation in the research.**
- (2) Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected.**
- (3) Other unexpected adverse events, regardless of severity, that may alter the Board's analysis of the risk versus potential benefit of the research *and*, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.** Examples of substantive changes that might need to be considered in response to this category of adverse events include: modification of inclusion or exclusion criteria to mitigate the newly identified risks; implementation of additional monitoring procedures of subjects; termination of enrollment of new subjects; modification of informed consent documents to include a description of newly recognized risks; and provision of additional information about newly recognized risks to previously enrolled subjects. (This should be considered for points 1 and 2 above.)
- (4) Unanticipated Problems** involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the Board.

Reporting of internal adverse events

The PI assesses whether the adverse event or unanticipated problem represents a reportable event as described above. If so, the PI must report it to the Board. For multicenter research, the PI should consult with the study sponsor or coordinating center regarding any changes to the protocol and/or informed consent documents being proposed by the PI. The PI also must ensure that the adverse event is reported to the central or independent monitoring entity in accordance with the monitoring plan described in the Board approved protocol.

The Board will review the PI's report using the same procedures described for reporting of external adverse events below.

The Board will report internal adverse events determined to be unanticipated problems to the supporting HHS agency head (or designee) and OHRP. These reports will include the

same type of information provided to the Board by the PI, along with a summary of the actions taken by the Board and institutional officials in response to the unanticipated problem(s).

If the PI determines that the **adverse event is an anticipated problem**, the PI needs to ensure that the internal adverse event is reported to a central or independent monitoring entity in accordance with the monitoring plan described in the Board approved protocol. If the monitoring entity subsequently determines, in contrast to the PI's determination, that the serious adverse event does represent an unanticipated problem, the monitoring entity should communicate this determination to the PI, who then should report the unanticipated problem to the Board.

Reporting of external adverse events

Reports of individual external adverse events occurring in subjects enrolled in multicenter studies do not necessarily have to be reported to the Board. Adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a central monitoring entity in accordance with the monitoring plan described in the Board approved protocol. When a central monitoring entity determines that a particular adverse event or series of adverse events **represents an unanticipated problem**, a report of the adverse event(s) must be submitted to the PI and the Board. If possible, reports of external adverse events submitted to the Board should present the adverse event in the context of the entire multicenter study. In addition, the local PI should consult with the study sponsor or coordinating center regarding any changes to the protocol and/or informed consent documents independently proposed by the local PI.

These central monitoring reports of external adverse events should include:

- 1) A clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and
- 2) A description of proposed actions to be taken by the investigators and/or IRB in response to the unanticipated problem (e.g., suspension of new subject enrollment, modification of the research protocol, and/or modification of the informed consent process).

Reports for which **no modifications** to the protocol or informed consent process/documents are needed, as determined by the IRB chairperson (or designee), may be handled as follows:

- 1) Filed in the IRB records without further review by the Board or,
- 2) Clarified through the following process: If the central monitoring entity or the PI did not propose any modifications to the protocol or informed consent process/document, but the Board Chair (or designee) believes that modifications are needed in response to the external adverse event(s), the IRB chairperson (or designee) requests in writing that the PI discuss the proposed modifications with the study sponsor or coordinating center and submit a response or necessary modifications for review by the Board or,
- 3) Referred, at the discretion of the Board Chair (or designee) to the rest of the Board members for review and further action, as appropriate, at a convened meeting.

Under HHS regulations at 45 CFR 46.109(a), the Board has authority to require submission of more detailed contextual information by the PI, the sponsor, the study coordinating center, or DSMB/DMC about any adverse event occurring in a research protocol as a condition of the continuation of the Board's approval of the research.

Reports requiring **modifications** to the protocol or informed consent process/documents are needed, as determined by the IRB chairperson (or designee), may be:

- 1) The Board Chair (or designee) requests in writing that the PI discuss the proposed additional modifications with the study sponsor or coordinating center and submit a response or the necessary additional modifications for review by the Board.
- 2) If all proposed modifications represent minor changes, the Board Chair (or designee) may review and, if appropriate, approve the modifications under an expedited review procedure (45 CFR 46.110(b)). All Board members are informed of the expedited approval (45 CFR 46.110(c)), and the report of the external adverse event will be filed in the IRB records.
- 3) If any of the proposed modifications represent more than a minor change, or if the Board Chair (or designee) determines for any reason that he or she should not approve the proposed modifications under an expedited review procedure, the proposed modifications will be forwarded to the other Board members for review at a convened meeting.

For any report of an external adverse event determined **to be an anticipated problem**, the PI maintains a copy of the external adverse event report and documentation of the basis for this determination. This record is to be made available to the Board on request.

Reports of Unanticipated problems (not related to adverse events) or Serious or Continuing Non-Compliance

Reports of unanticipated problems which are not or may not be related to adverse events must be reported to the Board in the same fashion as described above for external and internal reporting of adverse events.

The Board, in addition to the reporting requirements specified below, may take action appropriate for the circumstances to protect the safety, welfare and rights of research subjects.

Time requirement for reporting adverse events and/or unanticipated problems to the Board

Investigators shall submit to the Board site-specific reports of reportable adverse events and/or unanticipated problems involving risks to subjects or others according to the time frames listed below (days are determined by date of discovery or notice to the PI):

External Adverse Events

Category of Adverse Event	Study Related (Possible/Probable/Definite)		Not Study Related (Unrelated/Unlikely)	
	Expected	Unexpected	Expected	Unexpected
Fatal Events (Grade 5)	5 working days	5 working days	5 working days	5 working days
Life-Threatening or disabling (Grade 4)	Summarize in continuing review report	10 working days	Summarize in continuing review report	Summarize in continuing review report
Severe and undesirable (Grade 3)	Not reportable to IRB	Summarize in continuing review report	Not reportable to IRB	Not reportable to IRB
Moderate and Mild (Grades 1 & 2)	Not reportable to IRB	Not reportable to IRB	Not reportable to IRB	Not reportable to IRB
Unanticipated Problem that is a Reportable Event	5 working days	5 working days	5 working days	5 working days

Internal Adverse Events

Category of Adverse Event	Study Related (Possible/Probable/Definite)		Not Study Related (Unrelated/Unlikely)	
	Expected	Unexpected	Expected	Unexpected
Fatal Events ² (Grade 5)	5 working days	5 working days	5 working days	5 working days
Life-Threatening or disabling (Grade 4)	10 working days	10 working days	Summarize in continuing review report	10 working days
Severe and undesirable (Grade 3)	Summarize in continuing review report	10 working days	Summarize in continuing review report	Summarize in continuing review report
Moderate and Mild (Grades 1 & 2)	Not reportable to IRB	Not reportable to IRB	Not reportable to IRB	Not reportable to IRB
Unanticipated Problem that is a Reportable Event	5 working days and reportable to HHS agency head and OHRP	5 working days and reportable to HHS agency head and OHRP	5 working days and reportable to HHS agency head and OHRP	5 working days and reportable to HHS agency head and OHRP

Board review of protocol related drug/device external adverse events

If an investigator is notified about an adverse event that occurred at another site in a study related to, but not the same as, the Case Cancer protocol, and the adverse event results in a change in the Case Cancer protocol, consent form, or the risk/benefit ratio, the adverse event must be reported within **10 working days** of learning of the event, and the protocol changes must be made and submitted to the IRB by the PI as soon as possible. The same rule applies if the change in the Case Cancer protocol is due to publication of the adverse events results from another study which has an impact on the Case Cancer protocol.

Adverse events which occur in another study (including fatal events) and which do not result in a

² Internal, fatal events (Grade 5) with attribution of possible, probably, or definite that occur greater than 30 days after the last dose of treatment must be reported to the Board for review within 5 working days.

change in the protocol, consent form, or the risk/benefit ratio for the Case Cancer study, do not need to be reported to the IRB but should be kept on file by the investigator.

Reporting and Board Review Procedure

The Board's review of an adverse event and/or unanticipated problem will include analysis of the following information:

- 1) The description of known or foreseeable adverse events and risks in the IRB-approved research protocol, any applicable investigator brochure, the current IRB-approved informed consent document, and other relevant sources of information, such as scientific literature, product labeling, and package inserts;
- 2) Any underlying diseases or conditions of the subject(s) experiencing the adverse event; and
- 3) A careful assessment of whether the adverse event is related or possibly related to subject's participation in the research study.

At the **time of continued review** for an IRB-approved protocol, the Board will request a summary of all serious adverse events (Grades 3, 4 and 5) determined to be anticipated problems to be included in continuing review reports submitted to the IRB by investigators. The summary should include a simple and brief statement as to whether there have been any unanticipated problems and whether adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and/or any investigator brochure.

Notification of Board Actions

The Board shall notify the investigator in writing of its actions in approving, disapproving or requiring changes to (in order to approve) the Cancer Research. A disapproval notice shall include the basis for the disapproval and provide an opportunity for the investigator to address the Board in person or in writing regarding its action. All written correspondence from the Case Cancer IRB will be signed by the Case Cancer IRB Chairperson or his designee who will be named by written correspondence.

In addition to all applicable notices, a report of all adverse events and/or unanticipated problems at UHC shall be reported in writing to UHC, Vice President & Deputy Counsel, Claims and Litigation, W.O. Walker Center, 10534 Euclid Avenue, 8th Floor, Cleveland, Ohio 44106-2205, Mail Stop 5082. A report of all adverse events and/or unanticipated problems at CCF shall be reported in writing to CCF General Counsel, 1950 Richmond Road, TR38 Office of General Counsel, Lyndhurst, Ohio 44124-3719.

Suspension or Termination of Approval of Cancer Research

The Board has the authority to suspend or terminate its approval of Cancer Research for any reason it deems appropriate (HHS 45 CFR 46.113; FDA 21 CFR 56.113), such as:

- the research is not being conducted in accordance with the currently-approved protocol, applicable rules and regulations or with the Board's requirements; or
- the research has been associated with serious harm to subjects; or
- the research creates a potential threat to the safety and welfare of patients or others.

Any suspension or termination of approval shall include a statement of the reasons for the Board's action and shall be reported promptly to:

- the PI and Sponsor of the research;
- Human Protection Administrators at Case, CCF, and UHC; and
- the OHRP (HHS 45 CFR 46.113) or FDA (21 CFR 56.113)

An Administrative Hold may be placed on a study and/or the PIs research activities, should there be noncompliance due to a missed deadline. However, this Hold may be in effect for only thirty (30) days. If the issue is not resolved within that time period, then reporting to institutional and Governmental agencies may take place.

Reporting to the Institution and Government Agencies

The administrative office of the Case Cancer IRB shall notify and cooperate with the Case Office of General Counsel and law departments of CCF and UHC when investigating and preparing reports relating to research. The Board shall promptly report to the Human Protections Administrator at Case, CCF, and UHC, and the appropriate officials at OHRP, and FDA:

- any unanticipated problems involving risks to human subjects or others;
- any instances of serious or continuing noncompliance with the federal regulations or the requirements and determinations of the Case Cancer IRB; or
- any suspension or termination of IRB approval (HHS 45 CFR 46.108(a); 46.103(b)(5)); (FDA 21 CFR 56.108 (b))

Operations of the Board

Scheduling of Meetings

Regularly scheduled meetings of the Board will be scheduled on a weekly basis except for holiday and vacation breaks. Additional meetings may be scheduled as necessary.

The Board Chairperson or designee shall conduct all meetings of the Board. Meetings shall be conducted in accordance with Robert's Rules of Order, Revised in the absence of formal adoption of other rules or procedures.

Review Process

1. Each Case Cancer IRB member must be provided with sufficient information to be able to actively and constructively participate in the protocol review.

Each protocol will be assigned to reviewers who will be responsible for a full review of all materials, and will lead the discussion of the protocol, consent, the complete grant application (as applicable) and the risk/benefit ratio. Other members will receive a copy of the consent document(s) and protocol as well as other documents pertinent to a meaningful review.

2. Review materials must be received by the membership a week in advance of the meeting to allow for adequate review of the materials.

Expedited Review Process

The Board may utilize an expedited review procedure as authorized by HHS 45 CFR 46.110; FDA 21 CFR 56.110 and ICH 3.3.5.

The Board may utilize the expedited review process for the following types of Cancer Research (HHS 45 CFR 46.110; FDA 21 CFR 110):

1. Minor changes in previously approved Cancer Research during the period of one year or less, for which approval is authorized.
2. Cancer Research activities involving no more than minimal risk and in which the only involvement of human subjects will be in one or more of the categories identified on the respective lists as published by the FDA and the DHHS:

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

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

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

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

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

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

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

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

(3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine 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) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures

involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

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

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

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

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

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

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

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

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

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

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

The Board Chairperson may conduct expedited review, and shall appoint experienced reviewer from among the members of the Board to conduct expedited review.

In reviewing the Cancer Research, the reviewers may exercise all of the authorities of the Board except disapproval. If the reviewers do not approve the research being reviewed, they must refer it to the full Board for action.

A list of Cancer Research that has been approved under the expedited procedure, including an explanation of the type of research activity and the action taken, shall be provided to the full Board as soon as practical after such expedited approval. Members participating in the expedited approval shall respond to questions from the Board concerning that approval.

The Board may not use the expedited procedure if its use of that procedure has been suspended or terminated by the FDA, OHRP or Case, or at CCF, or at UHC if suspended or terminated by CCF or UHC, respectively.

Voting Requirements

A quorum is required to conduct business or review Cancer Research. A quorum requires a majority of the members or alternates of the Board to be present; provided however, that a quorum shall exist only if at least one faculty, medical staff member or employee of each Case, CCF and UHC is present for purposes of providing local context at such institution. Alternates with appropriate backgrounds may replace regular members to achieve the quorum.

At least one scientific and one non-scientific member must be present at all meetings in which research activities are being considered.

At least one physician member must be present when research activities involving drugs, biologics or devices are being considered.

Only members and alternates may vote.

No one may vote who has a conflict of interest with respect to the research under consideration.

A favorable vote of the majority of the members/alternates present is required to approve research activities. No votes will be permitted by proxy.

If necessary, Case Cancer IRB meetings may be conducted via telephone conference call provided each participating member has received all pertinent materials prior to the meeting and can actively and equally participate in the discussion of all protocols. Minutes of such meetings must clearly document that these two conditions have been satisfied in addition to the regulatory requirements.

The Case Cancer IRB will ensure and document a quorum for each protocol review.

Case Cancer IRB Actions

The IRB may vote to approve, approve with stipulations, disapprove, or table a research protocol. These actions, described below, require the vote of a majority of the members present at the meeting. A Case Cancer IRB member may abstain from voting for any reason, without explanation. Case Cancer IRB members who are sub-investigators on reviewed protocols shall recuse themselves from discussion and voting on the reviewed protocol and are also excused from the meeting prior to the vote of the Case Cancer IRB. A member may change his/her vote until the time the vote is finally announced by the Chairperson. After that, a member's vote may be changed only by permission of the Board which may be given by general consent (see Roberts Rules of Order, Revised Article VIII, Section 46).

The actions that may be taken by the Case Cancer IRB are as follows:

1. Approve the protocol (unconditionally).

The Board accepts the project as presented, finding it meets the requirements as previously outlined. The approval covers both the protocol and the Informed Consent document.

2. Approve the protocol with stipulations.

This action requires that modifications be made to some part of the proposed protocol or that certain information be placed on file with the Board. Modifications or "stipulations" set by the Board may include revising the consent form to explain the procedures or the voluntary nature of participation more clearly, devising mechanisms to maintain confidentiality, using specified safeguards in the procedures, submitting the approval from another institution that is collaborating on an aspect of the Cancer Research involving Human Subjects, or other changes as deemed necessary. The response to stipulations shall be returned to the full Board except that such response may be referred to the Chair/Deputy or designee when administrative review/verification of specific minor changes by the Chair or designee has been approved by the full Board.

3. Table the protocol.

This occurs when the Board feels it has insufficient information to take action, when waiting for full Board review of stipulations to set an approval date, or when the research design contains dangers and needs to be revised to minimize risk to human subjects.

4. Disapprove the protocol.

In this case the Board makes the decision that the potential benefits of the research do not outweigh the risks to the subjects and the research cannot be conducted as written.

Communication from the Board

The Board shall notify the investigators, the institution and the Human Protections Administrators of UHC and CCF in writing of its decision to approve or disapprove the proposed Cancer Research activity or of modifications required to secure Board approval of the Cancer Research activity, as well as the Board's determination that any Cancer Research is exempt.

The Board shall inform all investigators of approved Cancer Research in their approval letter that they must comply with the following:

1. Conduct the Cancer Research as required by the Protocol and in accordance with all applicable grants, contracts and policies at the institution where the research activity will be conducted.
2. Use only the Consent Form approved by the Board and provide directions for re-consenting if applicable.
3. Provide non-English speaking patients with a certified translation of the approved Consent Form in the patient's first language.
4. Obtain pre-approval from the Board of any changes in the research activity (except when necessary to protect human subjects; (HHS 45 CFR 46.103(b)(4); FDA 21 CFR 56.108(a)(3)); immediately report to the Board any such emergency changes for the protection of human subjects.
5. Within 48 hours, report in writing to the Board the death, hospitalization, or serious illness of any study subject enrolled in a Case Western Reserve University IRB-approved protocol.
6. Within 48 hours, promptly report to the Board any new information that may adversely affect the safety of the subjects or the conduct of the trial.
7. Provide reports to the Board concerning the progress of the research, when requested.
8. Obtain pre-approval of study advertisements from the Board before use.
9. Conduct the informed consent process, without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate.

If the Board decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. (HHS 45 CFR 46.109(d); FDA 21 CFR 56.109(e); ICH 3.1.2 and 3.3.9).

Record Requirements

The Board shall keep all required records and reports specified by regulation and these Written Procedures (HHS 45 CFR 46.115; FDA 21 CFR 56.115; ICH 3.1.2, 3.4) and applicable grant, contract, or policy at CCF or UHC.

Administrative staff shall maintain documentation of Board activities, including the following.

- Copies of all Cancer Research proposals reviewed
- Scientific evaluations, if any, that accompany the proposal
- Approved consent documents
- Progress reports submitted by research investigators
- Reports of injuries to subjects
- Adverse reaction reports and documentation of Case Cancer IRB review of these reports
- Minutes of Board meetings
- List of Board members and their Alternates
- Records of continuing review activities
- Copies of all correspondence between the Board and the research investigators
- Statements of significant new findings provided to subjects as required by HHS 45 CFR 116(b)(5), FDA 21 CFR 50.25(b)(5) and ICH 4.8.2.
- Emergency use reports

Minutes of Board meetings shall be in sufficient detail to show:

- Names of attendees at the meetings (including guests)
- Actions taken by the Board, and the vote on these actions including the number of members voting for, against, and abstaining
- Basis for requiring changes in or disapproving research
- Written summary of the discussion of controverted issues and their resolution
- Dissenting reports and opinions

List of Board members and their alternates identified by:

- Name
- Earned degrees
- Representative capacity
- Indications of experiences such as board certifications, licenses, etc.
- Information sufficient to describe each member's chief anticipated contributions to the Board deliberations
- Any employment or other relationship between the member and Case., CCF or UHC.

Records relating to a specific research activity shall be maintained for at least 3 years after completion of the research (HHS 45 CFR 46.115(b); FDA 21 CFR 56.115(b); ICH 3.4) and as required by any grant, contract or policy at CCF or UHC..

Board records shall be accessible for inspection and copying by authorized representatives of FDA, the Office for Human Research Protections (OHRP) or other agencies, when appropriate jurisdiction exists, at reasonable times and in a reasonable manner (HHS 45 CFR 46.115(b); FDA 21 CFR 56.115(c); ICH 3.4). The Board shall also fully cooperate with any audit or request for inspection or copying of records, by CCF or UHC.

Information the Investigator Provides to the Board

A current CV containing qualifications by education, training and experience to conduct the research submitted for review may be requested by the Case Cancer IRB.

A description of facilities and support staff that will be used for the research.

A complete copy of the Protocol or Federal grant application or proposal (when applicable) and written disclosure of any conflicts of interest relating to the research.

Study information which includes or addresses the following, as applicable:

- Title of the study
- Purpose of the study which includes expected benefits
- Sponsor of the study
- Results from previous related research
- Subject inclusion/exclusion criteria
- Justification for inclusion of any special or vulnerable subject population such as children or prisoners
- Study design which includes a discussion of the appropriateness of the research methods
- Description of data safety monitoring plans
- Description of procedures to be performed
- Provisions for managing adverse reactions
- Circumstances surrounding the consent procedure, including vulnerable populations, language difficulties, subject autonomy
- Procedures for documenting informed consent including any assent for minors, use of witnesses, need for translation
- Payment to subjects for their participation
- Any compensation for injuries to research subjects
- Provisions for protecting subject privacy
- Extra costs to subjects for participation in the study
- Extra costs to third party payers because of a subject's participation

- Proof of receipt of approval from Case, CCF, and/or UHC Committees, including Conflict of Interest, BioSafety, Radiation Safety, Pharmacy or Protocol Review and Monitoring Committees, as appropriate.
- Complete conflict of interest disclosure.
- Investigator Brochure (when one exists)
- The case report form (when one exists)
- Proposed informed consent document that contains the elements identified in HHS 45 CFR 46.116; FDA 21 CFR 50.25 and these Written Procedures
- Requests for changes to the study after initial approval
- Reports of unexpected adverse events (death, hospitalization or serious illness of any research subject)
- Progress reports when requested
- Final report
- Other forms or reports required by the Board or the institution at which the research activity will be conducted
- Any and all subject advertisements and recruitment procedures including incentive programs

Appendix A

As taken from the Office for Human Research Protections (OHRP) draft guidance on reporting and reviewing adverse events and unanticipated problems involving risks to subjects or others, an **adverse event** can be defined as follows:

- 1) Any undesirable and unintended, although not necessarily unexpected, effect of the research occurring in human subjects as a result of (a) the interventions and interactions used in the research; or (b) the collection of identifiable private information under the research.
- 2) Any occurrence of injury, dysfunction, disease, or abnormality of any organ or tissue that occurs in a human subject enrolled in a research protocol. Manifestations of an adverse event may include symptoms, physical exam abnormalities, diagnostic study abnormalities, and/or death.
- 3) Any untoward medical occurrence in a human subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the product, whether or not considered related to the product.
- 4) Any untoward sign, result, event, misadventure, injury, dysfunction, adverse drug reaction, or other undesirable happening that involves any human subject regardless of whether it was listed in the informed consent document as an expected risk.
- 5) Any untoward physical or psychological occurrence in a human subject participating in research. An adverse event can be any unfavorable or unintended event including abnormal laboratory finding, symptom, or disease associated with the research. An adverse event does not necessarily have to have a causal relationship with the research or any risk associated with the research or the research intervention, or the assessment.
- 6) An adverse drug experience as defined by FDA regulations at 21 CFR 314.80(a) - Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.
- 7) An adverse experience as defined by FDA regulations at 21 CFR 600.80(a) – Any adverse event associated with the use of a biological product in humans, whether or not considered product related, including the following: an adverse event occurring in the course of the use of a biological product in professional practice; an adverse event occurring from overdose of the product whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacological action.

- 8) A life-threatening adverse drug experience as defined by FDA regulations at 21 CFR 312.32 – Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- 9) A life-threatening adverse experience as defined by FDA regulations at 21 CFR 600.80(a) – Any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- 10) An unanticipated adverse device effect as defined by FDA regulations at 21 CFR 812.3(s) – Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, 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.
- 11) An unexpected adverse drug experience as defined by FDA regulations at 21 CFR 312.32(a) – Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.