

**University of California, Irvine
Human Research Protections
Standard Operating Policies and Procedures**

Policy Number: 41

Title: Investigational Drugs, Agents, and Biologics

**Date of Last of Revision: 07/28/2006; 07/22/2010; 04/19/2012; 10/17/2012; 05/01/16;
10/06/17; 04/01/19; 04/12/22**

Policy:

It is the policy of the UC Irvine (UCI) Institutional Review Board (IRB) that the use of investigational drugs, agents, and/or biologics be reviewed and approved for use in accordance with the federal regulations (the United States Food and Drug Administration (FDA)) and the Department of Health and Human Services (DHHS)).

I. UCI IRB Requirements for the Use of an Investigational Drug, Agent, or Biologic

- A. The UCI IRB conducts initial approval and on-going monitoring of all investigational drugs, agents, and biologics used in human subjects research under its authority.
- B. Prospective IRB review is required even if a waiver from IRB regulations has been granted by the FDA for use of the investigational drug, agent, or biologic.
- C. Prospective review by the convened IRB is required for the use of an investigational drug, agent, or biologic as part of the Right to Try (RTT) Act.
- D. UCI will not provide investigational devices to patients outside of the FDA's expanded access program.
- E. Research that involves the use of a drug other than a marketed drug in the course of medical practice must have an Investigational new drug (IND) number, unless the protocol meets the five exemptions from the requirement of an IND per 21 CFR 312.2(b).
 1. The criteria is as follows:
 - a) Use of the investigational drug, agent, or biologic is not intended to be reported to the FDA in support of a new indication for use nor support any significant change in labeling for the product;
 - b) The use of the investigational drug, agent, or biologic is not intended to support a significant change in the advertising of the product;
 - c) The use of the product does not involve a route of administration, dosage level, and/or use in a subpopulation, or other factors that significantly increase the risks, or decrease the acceptability of the risks associated with the use of the drug, agent, or biologic;
 - d) The use will be conducted in compliance with the IRB approval and informed consent procedures;
 - e) The use will be conducted in compliance with the requirements concerning the promotion and sale of the drug, agent, or biologic as described in FDA regulations 21 CFR Sec. 312.7;

2. It is important to note that the above does not intend to invoke exception from informed consent requirements for emergency use.
- F. FDA regulations allow certain individuals not enrolled in clinical trials to obtain **expanded access** to investigational drugs, agents, or biologics through the following methods:
1. **Compassionate Use**: The term “compassionate use” is erroneously used to refer to the provision of investigational drugs outside of an on-going clinical trial to a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term “compassionate use” does not, however, appear in FDA or DHHS regulations. It is preferable, instead, to use the names of the specific access programs when discussing the use of investigational articles outside of formal clinical trials. Prospective IRB review and approval is required.
 2. **Group C Treatment Investigational New Drug (IND)**: The "Group C" treatment IND was established by agreement between the FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally Phase 3 study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. They can generally be administered by properly trained physicians without the need for specialized supportive care facilities. Group C drugs are distributed only by the National Institutes of Health under NCI protocols. Although the FDA typically grants a waiver for most drugs used in Group C Treatment IND protocols, the UCI IRB requires prospective IRB review and approval.
 3. **Open – Label Protocol**: A study designed to obtain additional safety data, typically done when the controlled trial has ended and treatment continues. The purpose of such a study is to allow subjects to continue to receive the benefits of the investigational drug, agent, or biologic until marketing approval is obtained. Prospective IRB review and approval is required.
 4. **Parallel Track**: A method approved by the FDA that expands the availability of investigational drugs, agents, or biologics as quickly as possible to persons with AIDS and other HIV-related diseases. These drugs, agents or biologics are utilized in separate protocols that “parallel” the controlled clinical trials and are essential to establish the safety and effectiveness of these new drugs, agents, or biologics. Although the Secretary of the DHHS may, on a protocol-by-protocol basis, waive the provisions of 45 CFR Part 46 where adequate protections are provided through other mechanisms, prospective IRB review and approval is required by the UCI IRB.
 5. **Treatment IND or Biologics**: A mechanism for providing eligible subjects with investigational drugs (as early in the drug development process as possible) for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. The FDA defines an immediately life-threatening disease as a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. The FDA will permit an investigational drug to

be used under a treatment IND after sufficient data have been collected to show that the drug “may be effective” and does not have unreasonable risks. Prospective IRB review and approval is required.

1. There are four requirements that must be met before a treatment IND can be issued:
 - a) The drug is intended to treat a serious or immediately life-threatening disease;
 - b) There is no satisfactory alternative treatment available;
 - c) The drug is already under investigation or trials have been completed; and
 - d) The trial sponsor is actively pursuing marketing approval.
2. The FDA identifies two special considerations when a patient is to be treated under a Treatment IND:
 - a) Informed Consent. Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications which have not been proven either safe or effective in a clinical setting. Both the setting and their desperation may work against their ability to make an informed assessment of the risk involved. Therefore, the IRB ensures that potential subjects are fully aware of the risks involved in participation.
 - b) Charging for Treatment INDs. The FDA permits charging for the drug, agent, or biologic when used in a Treatment IND. Therefore, the IRB Committee pays particular attention to Treatment INDs in which the subjects will be charged for the cost of the drugs. If subjects will be charged for use of the test article, economically disadvantaged persons will likely be excluded from participation. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles. The IRB balances this interest against the possibility that unless the sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA approval.
6. **Single-Patient Use:** The use of an investigational drug outside of a controlled clinical trial for a patient, usually in a desperate situation, who is unresponsive to other therapies or in a situation where no approved or generally recognized treatment is available. There is usually little evidence that the proposed therapy is useful but may be plausible on theoretical grounds or anecdotes of success. Access to investigational drugs for use by a single, identified patient may be gained either through the sponsor under a treatment protocol, or through the FDA, by first obtaining the drug from the sponsor and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment use. Prospective IRB review and approval by an IRB Chair is required.
7. **Emergency IND:** The emergency use of an unapproved investigational drug, agent, or biologic requires an emergency IND. The FDA has established mechanisms and guidance for obtaining an Emergency IND for the use of investigational drugs, agents, or

biologics. Additional UCI IRB guidance regarding emergency IND is provided in IRB Policy 45.

8. **IND Exemptions in the Treatment of Cancer:** The FDA allows for an Investigational New Drug (IND) exemption of studies of lawfully marketed drug products for the treatment of cancer. When determining if an IND needs to be submitted to study marketed drugs for treating cancer, Researchers must apply the exemption criteria listed in 21 CFR 312.2(b)(1)(i-v). Additionally, planned studies may be considered exempt from the requirements of an IND if the studies involve a new use, dosage, schedule, route of administration, or new combination of marketed cancer products in a patient population with cancer and the following conditions apply:

- a) The studies are not intended to support FDA approval of a new indication or a significant change in the product labeling.
- b) The studies are not intended to support a significant change in the advertising for the product.
- c) Investigators and their IRBs determine that, based on scientific literature and generally known clinical experience, there is no significant increase in the risk associated with the use of the drug product.
- d) The studies are to be conducted in compliance with the IRB and informed consent regulations, pursuant to parts 50 and 56.
- e) The studies will not be used to promote unapproved indications in compliance with 21 CFR 312.7.

- G. Where a protocol is subject to review under more than one department or agency's regulations, the requirements of each set of regulations must be met. This situation may arise, for example, with Treatment Investigational New Drugs where both the FDA and DHHS have jurisdiction over the research. The use of an unapproved investigational drug, agent, and/or biologic requires an FDA IND.

- H. **Right to Try (RTT):** In May 2018, the federal Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017 was signed into law, creating a federal framework for patients to access investigational new drugs and biologics outside of clinical trials and outside of the U.S. Food and Drug Administration's (FDA) expanded access program. The Federal Right to Act enables a patient with a "life-threatening" disease or condition to access investigational drugs and biologics that have completed Phase 1 testing under an FDA-approved clinical trial and which are either being actively developed or produced by the manufacturer or not placed on clinical hold. Importantly, the federal law does not address the use of investigational devices.

1. In order to receive an investigational drug or biologic under the federal RTT Act, the patient must:

- a) Have a life-threatening disease or condition;
- b) Have exhausted treatment options, as certified by the physician;
- c) Be unable to participate in a clinical trial involving the investigational drug, as certified by the physician; and

- d) Have given his or her written informed consent (or consent of a legally authorized representative) to the treating physician regarding use of the investigational drug.
2. Use of an investigational drug under the RTT is exempt from FDA requirements for review and authorization, so long as the sponsor or manufacturer of the drug is in compliance with FDA requirements applicable to investigational drugs. Note that the law does not limit compliance to the specific investigational drug that is the subject of the use.
 3. The RTT act does require sponsors and manufacturers who have made their investigational drugs available under RTT to annually report to the FDA the number of doses supplied, the number of patients treated, the uses for which the drug was made available, and any known serious adverse events. In turn, the FDA must make this information publicly available on its website.
 4. Patients may be charged the direct costs of making the investigational drug available for their use.
 5. The federal RTT does incentivizes sponsors and manufacturers to make their investigational drugs available by protecting them against liability with respect to acts and omissions regarding the investigational drug. The Act also protects prescribers, dispensers, and other individuals from liability, unless the act or omission constitutes reckless or willful misconduct, gross negligence, or an international tort under state law. Finally, the Act expressly protects against liability to any person for not providing access to an investigational drug under the Act.
 6. The California RTT Act is similar to the federal Act, though there are notable differences.
 - a) In one respect, the California law is broader than the federal right to try law as it applies to use of investigational drugs, biologics and devices that have successfully completed an FDA-regulated Phase 1 trial and remain under active investigation by the FDA. The federal law does not include devices.
 - b) In most instances, the California law imposes more requirements to obtain access to an investigational drug outside of a clinical trial.
 - c) California RTT limits access to patients with an “immediately life-threatening disease or condition”, whereas the federal law only requires patients have a “life-threatening disease or condition.” Thus, under state law, the patient must be in a stage of disease in which there is a reasonable likelihood death will occur in a matter of months.
 - d) The treating physician and a second consulting physician must both recommend that the patient receive the investigational product, attest to this recommendation, and attest that the patient meets the criteria of the state law.
 - e) Specific informed consent requirements must be met. Like the federal law, a surrogate may consent on behalf of the patient consistent with California law requirements. However, the

consent form must contain the information from the California Health and Safety Code - Section 111548.1(h)(1), and also must meet the requirements set forth in the California Protection of Human Subjects in Medical Experimentation Act.

- f) An IRB must review and approve the protocol and consent form.
 - (1) At UCI a Prospective review by the convened IRB is required per UC Office of the General Counsel Health Sciences Research Advisory guidance.
 - g) Reporting requirements between the federal and California RTT Acts also differ. While federal law requires that the sponsor or manufacturer make information available to the FDA (which the FDA must publicly post), the California law imposes an obligation upon the IRB of record to biannually report information regarding the number of requests made to the IRB for an investigational product, the status of each request, the duration of treatment, the costs of treatment paid by patients, the success or failure of the investigational product in treatment, and adverse events.
 - h) Similar to federal law, California RTT does not impose an obligation upon manufacturers to make an investigational product available to a patient. California RTT also provides that a manufacturer may recover the costs of the manufacture of the product. However, the law removes any liability upon the patient's heirs or the patient's health benefit plan, for any outstanding debt related to the treatment using the investigational product.
 - i) In addition, the CA RTT specifically prohibits the Medical Board of California and the Osteopathic Medical Board of California from taking any disciplinary action against a physician's license to practice medicine based solely upon the physician's recommendation to treat or treatment of a patient with an investigational product, so long as the protocol was approved by an IRB. The Act also provides that any actions taken pursuant to the state law by a manufacturer or any other person or entity involved in caring for the patient cannot serve as the basis for any civil, criminal or disciplinary claim or cause of action under state law.
- 7. Given the stricter California law requirements for using an investigational drug without FDA approval (IRB review and approval is required) and the additional protection the California law affords to physicians regarding licensure, UCI will comply with California's RTT law requirements.
 - 8. Because the federal RTT law does not address the use of investigational devices UCI will not provide investigational devices to patients outside of the FDA's expanded access program.

II. **Use of an Investigational Drug, Agent, or Biologic by a Researcher**

- A. In order for an investigational drug, agent, or biologic to be used in clinical research at UCI, an IND number must be issued by the FDA.

- B. A valid IND number is required (e.g., listed on Sponsor Protocol or a copy of the FDA approval of the IND). The UCI IRB may review research without an IND number but will not grant approval until documentation of an IND number is provided to the IRB.
- C. Researchers provide information regarding the use of investigational drugs, agents, and biologics as required in the IRB Application for human research.
- D. Clinical investigations of a drug, agent, or biologic that is lawfully marketed in the United States are exempt from the requirements of an IND as per 21 CFR 312.2(b).
- E. Research involving combinations of FDA approved drugs, agents, or biologics that are currently approved as single use, do not require an IND. However, use of these drugs, agents, or biologics in clinical research must still be prospectively reviewed and approved by the IRB.
- F. The Investigator administering an investigational drug, agent or biologic must meet the following requirements in order to use an investigational drug, agent, or biologic in research conducted under the jurisdiction of the UCI IRB:
 1. The drug, agent, or biologic must be used only in accordance with the plan of investigation as described in the FDA-approved IND application and the IRB- approved protocol;
 2. The drug, agent, or biologic may only be used in participants under the LR's supervision or under the supervision of a physician who is a Co-Researcher; and
 3. Informed consent from the participant or the participant's surrogate decision-maker is prospectively obtained, unless a waiver of consent has been approved by the UCI IRB.
- G. Investigators using an investigational drug/biologic are required to provide a plan about how the drug/biologic will be managed and controlled in the IRB Application. Investigators are required to:
 1. Describe how the Investigator will ensure that the investigational drug/biologic is used only in accordance with the UCI IRB approved protocol.
 2. Explain who will access to the drug/biologic and how access will be controlled to secure the drug/biologic.
 3. Explain how records for control of the drug/biologic will be recorded. For example, use of the sample Drug/Biologic Accountability Log provided on the Human Research Protections website; use of the Drug/Biologic Log provided by the Sponsor; or no log will be used and the researcher must provide justification.
- H. **Research with the use of an investigational drug, agent, or biologic must be conducted in accordance with all UC, UCI and UCI IRB policies and procedures.**
- I. All initial requests for IRB approval of a study that include the use of an investigational drug, agent, or biologic will be reviewed and approved by the full IRB Committee.

- III. **Use of an Investigational Drug, Agent, or Biologic by an Investigator Assuming the Sponsor Function**
- A. In rare instances, a UCI Investigator will assume the Sponsor function for use of an investigational drug, agent or biologic. A *Sponsor-Investigator* is an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.
 - B. In addition to the requirements above, the UCI Investigator must submit a copy of the FDA Notice of Claimed Investigational Exemption for a New Drug (IND Application) along with their IRB Application for review. UCI IRB approval will not be granted until documentation of a valid IND number is submitted to the IRB.
 - C. The UCI Investigator must comply with all Sponsor function requirements described in 21 CFR 312.
- IV. **Advertising or Recruitment for Studies Involving Investigational Drugs, Agents, or Biologics (See HRP Policy # 22)**
- A. Advertisements or recruiting tools must not include the term “new treatment”, without explaining that the drug, agent, or biologic is “investigational”, meaning non-FDA approved. A phrase such as “receive new treatment” implies that all study subjects will be receiving newly marketed products of proven worth. It is not a treatment since its effectiveness has not been proven or established. The term “new” is misleading as it gives the participant hope of a new intervention when the outcome is unknown. This could be viewed as coercive.
 - B. Advertisements or recruiting materials must not include the promise of “free medical treatment” when the intent is only to say that participants will not be charged for taking part in the investigation or experimental intervention (e.g., drug, agent, biologic). The use of the word “free” could be viewed as unduly influential as it may entice someone to participate in a study for the perceived benefits.
- V. **Informed Consent in Research that Involves an Investigational Drug, Agent, or Biologic**
- A. Informed consent must meet the requirements outlined in the IRB Informed Consent policies and procedures (See HRP Policy # 30);
 - B. No claims are to be made which state or imply, directly or indirectly, that the investigational drug, agent, or biologic is safe or effective for the purposes under investigation or that the drug is in any way superior to another drug;
 - C. The informed consent document must contain a statement that the drug, agent, or biologic is “investigational” or “experimental”;
 - D. The informed consent document must contain a statement that the FDA may have access to the participant's medical records as they pertain to the study; and
 - E. The researcher must assure that throughout the consenting process and study participation the participant understands that the investigational drug, agent, or biologic is under investigation, and that its benefits for the condition under study are unproven.

References:

21 CFR 50

21 CFR 56

21 CFR 210

21 CFR 211

21 CFR 312

45 CFR 46

U.S. Food and Drug Administration Information Sheet: Investigational Use of Marketed Drugs, Biologics and Medical Devices, 1998.

U.S. Food and Drug Administration: Expanded Access of Investigational Drugs, 1998.

FDA Guidance Sheet: IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer, January 2004

UC Office of the General Counsel Health Sciences Research Advisory: *Clinical Use of Investigational Drugs, Devices and Biologics under Federal and California Law*, November 2018

California Right to Try Act: AB-1668 Investigational drugs, biological products, and devices.

UCI Health Management of Investigational Medications Policy, March 2021

Procedure Number: 41.A

Title: Procedure for Review of Research Involving Investigational Drugs, Agents, and Biologics

Procedure:

This procedure outlines the review and approval process for use of investigational drugs, agents, and biologics in clinical research.

I. Lead Researcher (LR) Responsibilities

- A. The LR will provide all information regarding the use of investigational drugs, agents, and biologics as required in the UCI IRB Application. This will include the identification of the IND number.
- B. When the LR holds the IND for the investigational drug, agent, or biologic, a copy of the FDA approval letter is required as part of the IRB submission.
- C. The LR must provide justification for each of the conditions required for a drug, agent, or biologic to be exempt from the requirements of an IND (See HRP Policy # 41). The IRB Committee will determine if the justification warrants exemption from IND requirements.
- D. **The Investigator will obtain and manage the drug, agent, or biologic in accordance with the UCI Health Management of Investigational Medications Policy.**
- E. The LR will complete the informed consent process unless a waiver has been granted by the IRB.
- F. The LR will maintain all study case report forms and drug dispensing records as required by the sponsor, Institution, and/or FDA.
- G. The LR will notify the IRB of any modifications, unanticipated problems to participants or others that may occur while conducting the research or follow-up.
- H. The LR will assure that unanticipated problems involving participants or others are reported to the IRB via the UCI New Information Report in accordance with HRP Policy # 19.
- I. The LR will complete and submit renewal applications in accordance with HRP policy at the designated review intervals imposed by the IRB.
- J. The Investigator will notify the FDA and IRB of closure or completion of the study and return all unused products per the sponsor's instructions.
- K. When requesting RTT, the LR will utilize and complete the following additional documents as found on the HRP webpage:
 - 1. The Treating Physician Checklist
 - 2. The Treating Physician Attestation
 - 3. The Consulting Physician Attestation
 - 4. Informed Consent for a Eligible Patient Seeking an Investigational Drug or Biologic Under Right to Try Act
 - i. Once approved by the IRB, within 30 days of beginning treatment, the LR will provide the following to IRB@research.uci.edu:
 - a) Provide a copy of the signed attestation.
 - b) Provide the following status as required to reporting to the State Department of Public Health, the Medical Board of

California, and the Osteopathic Medical Board of California:

1. The duration of the treatment.
2. The costs of the treatment paid by eligible patients.
3. The success or failure of the investigational drug, biological product, or device in treating the immediately life-threatening disease or condition from which the patient suffers.
4. Any adverse event for each investigational drug, biological product, or device.

II. **IRB Committee Responsibilities**

- A. All initial requests for IRB approval of a study that includes the use of an investigational drug, agent, or biologic will be reviewed and approved by the full IRB Committee.
- B. When research involves a drug with an IND, the IRB Committee, together with the IRB Administrator, should evaluate whether the IND number is valid for the proposed use. The purpose of this verification is to prevent situations where researchers may begin FDA- regulated research that require an IND before the FDA has issued an IND number.
- C. If the LR is requesting the drug, agent, or biologic be exempt from IND requirements, the IRB Committee must discuss each of the conditions for an exemption and determine if the LR's justification meets the criteria for exemption from the IND requirements.
- D. The assigned reviewers of the research protocol involving drugs, agents, or biologics will seek clarification from a UCIMC pharmacy representative of any concerns that may affect the risk/benefit assessment.
- E. The full IRB Committee will review the proposed research, informed consent documents (including notification that the FDA may have access to the participant's study records), the procedure for obtaining informed consent, and additional information, when applicable, to determine whether the study meets criteria 45 CFR 46.111 and 21 CFR 56.111 for approval.
- F. The IRB Committee must first consider whether the protocol is scientifically sound. The following aspects of the study should be considered when making a determination regarding risk/benefit ratio:
 1. Prior reviews by the FDA, other institutions, scientific review committees, funding agencies (e.g., NIH), or others; and
 2. Study design which includes the study population, the trial phase, and mechanisms for data analysis and surveillance.
- G. Submission of amendments, unanticipated problems to participants or others, and renewals will be reviewed at the level for which the criteria are met.
- H. Final IRB approval is evidence that the study meets criteria 45 CFR 46.111 and 21 CFR 56.111 as noted above and is documented in the IRB approval letter.

III. **IRB Administrator (or designee – e.g., Senior Analyst) Responsibilities**

- A. The Administrator will pre-review and request any necessary revisions for submitted documents for use of investigational drugs, agents, or biologics as outlined for new IRB Applications.

- B. The Administrator will verify that additional documents have been submitted by the LR as required:
 - 1. Any supplemental information regarding the investigational drug, agent, or biologic supplied by the sponsor.
- C. When research involves a drug with an IND, the IRB Committee, together with the IRB Administrator, should evaluate whether the IND number is valid.
 - 1. Validation of an IND can be done by:
 - a) Determining that the IND number in the IRB Application matches the Sponsor Protocol or
 - b) Upon receipt of communication from the Sponsor, which corresponds with the IND number provided in the IRB Application or
 - c) Upon receipt of communication from the FDA, which corresponds with the IND number provided in the IRB Application
 - 2. Validation of an IND *should not* involve:
 - a) Confirmation of the IND number by referencing the Investigator's Brochure (IB). This is because one IB often serves multiple IND's.
- D. Once the LR has met all the requisite requirements, the Administrator will place the new study on the next available Committee agenda.
- E. If the LR is requesting the drug, agent, or biologic be exempt from IND requirements, the Administrator must document the IRB Committee's discussion and determination for each of the conditions required for an exemption from the IND requirements.
- F. The Administrator will assist reviewers in obtaining additional information that may be requested regarding the investigational drug, agent, or biologic from the LR.
- G. For Investigator Initiated Research, the Administrator will ensure that final IRB approval is not released until the protocol has been reviewed and approved by UCI Investigational Drug Services (IDS).**
 - 1. IDS has administrative access to the electronic IRB submission and management system to help facilitate this process.
- H. The Human Research Protections (HRP) staff will process all requests for amendments, unanticipated problems to participants or others, and continuing reviews per corresponding IRB policies and procedures.
- I. The HRP staff will update and maintain current information in the electronic IRB submission and management system.