CARILION CLINIC INSTITUTIONAL REVIEW BOARD
Standard Operating Guidelines

Title: 4.1: Investigational Drugs and Biologics: USE OF INVESTIGATIONAL DRUGS/BIOLOGICS, INVESTIGATIONAL USE OF FDA-APPROVED DRUGS/BIOLGICS, INVESTIGATIONAL NEW DRUG APPLICATION (IND)	
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Objective:

To set forth guidance for the Carilion Institutional Review Board (IRB) submission, review, and approval of research involving the use of investigational drugs, and the investigational use of FDA-approved drugs or biologics. To provide guidance regarding Investigational New Drug Applications (IND).

General Description:

Clinical investigations involving drugs or biologics which are not FDA-approved for marketing must be reviewed and approved by the Food and Drug Administration (FDA). The FDA approval process involves filing an Investigational New Drug Application (IND) with the FDA, according to 21 CFR Part 312.

There are three IND types:

- Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician may submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

Any clinical investigation of an FDA-approved drug/biologic and use of an IND requires prior IRB approval, except in the rare care of an Emergency Use. The IRB approval process involves a submission to the IRB to include an IRB application, all materials related to the use of the drug or biologic, and informed consent document.

Procedure:

Clinical Investigations of Drugs or Biologics

IRB approval is required if the intended use of a drug or biologic involves a clinical investigation. The investigator and/or sponsor who plans to use a drug or biologic in a clinical investigation must first determine whether it is necessary to apply to the FDA for an IND for the intended use of the product. It is important to consult with the IRB during the research design to assist with

this decision and the submission process. The IND and IRB submission may happen concurrently, but final IRB approval is contingent upon FDA.

Whether an IND is needed to conduct a clinical investigation primarily depends on the intent of the investigation and the degree of risk associated with the use of the drug in the investigation.

An IND is required for the following uses:

- Any use of a drug or biologic not approved for marketing by the FDA, even if no investigation is being conducted.
- Studies involving a drug or biologic that is not approved by the FDA.
- Studies involving an approved (i.e., commercially available) drug or biologic that is being tested to support a new indication or significant change in labeling of the drug or biologic.
- Studies involving an approved drug or biologic that is being tested to support a significant change in advertising for the drug or biologic.
- Studies involving an approved drug or biologic that is being used or tested in a new route of administration, new dosage level, or new patient population that may increase the risk, or decrease the acceptability of the risks, of the drug or biologic.

A clinical investigation of a drug/biologic that is lawfully marketed in the United States is exempt from the IND requirements if all of the criteria in 21 CFR 312.2(b) are met:

- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug;
- If the drug is lawfully marketed as a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug;
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii));
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50);
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

Other exemptions:

- Off-Label Use (unlabeled indication) of a lawfully marketed drug or biologic as long as the use is strictly for clinical purposes, and the results are not collected for or presented as a clinical investigation.
- A clinical investigation involving blood grouping serum, reagent red blood cells, or anti-human globulin.
- A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.
- A drug intended solely for tests in vitro or in laboratory research animals.

An IND application may go into effect:

- 30 days after FDA receives the application, unless FDA notifies the sponsor that the investigations described in the application are subject to a clinical hold; or
- on earlier notification by FDA that the clinical investigations in the IND may begin.

Once an IND application is in effect, a drug manufacturer may ship the investigational new drug to the investigator(s) named in the application. An investigator may not administer an investigational new drug to human subjects until the IND application goes into effect.

Full Board Review
Clinical investigations utilizing drugs/biologics generally involve more than minimal risk. The initial review of these studies will be conducted at a convened meeting of the full board unless the study qualifies as minimal risk.

Responsibilities for control of investigational drugs/biologics
Investigators conducting studies in which an investigational drugs/biologics will be used are responsible for control, handling, monitoring, and accountability to the FDA as outlined in 21 CFR 312.50 and 21 CFR 312.60. Please refer to the obligations of investigators and sponsors in 21 CFR 312.64.

Reporting Requirements
When an IND is issued, there are federal requirements for reporting adverse events (AEs) and other safety information to the FDA and the IRB. Investigators must report certain adverse events and other reportable events directly to the IRB within 7 business days. When the study sponsor holds the IND, investigators need to report all AEs to the sponsor and the sponsor will submit appropriate reports to the FDA.

An IND may be submitted for one or more phases of an investigation
Phase 1-includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.
Phase 2- includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.
Phase 3- studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

Open Label Protocol or Open Protocol IND

These are usually uncontrolled studies, carried out to obtain additional safety data (Phase III studies). They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective IRB approval.

Emergency Use of an Investigational Drug or Biologic

Emergency IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for prior submission of an IND in accordance with 21 CFR 312.23 or 312.20. In such cases, FDA may authorize shipment of the drug for a specified use

[21 CFR 312.310]. Such authorization is usually conditioned upon the sponsor filing an appropriate IND application as soon as practicable. 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.

Requests for FDA authorization may be made by telephone or other rapid communication means [21 CFR 312.310] **PLEASE SEE TABLE AT END OF DOCUMENT**

Emergency Exemption from Prospective IRB Approval

The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

The IRB should be notified prior to such use; however, this notification should not be construed as an IRB approval. Notification should be used by the IRB to initiate tracking to ensure that the investigator files a report within the five-day timeframe required by 21 CFR 56.104(c). The FDA regulations do not provide for expedited IRB approval in emergency situations. An IRB must either convene and give full IRB approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires an IRB approval letter before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, the IRB may provide the sponsor with a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although this is not an IRB approval, the acknowledgment letter has been acceptable to manufacturers and will allow the shipment to proceed.

Use the Single Patient Emergency Use Form and submit to the IRB. Subsequent use of the test drug must be reviewed by the IRB.

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 a physician who is not otherwise participating in the clinical investigation certify in writing all of the following [21 CFR 50.23(a)]:

- The subject is confronted by a life-threatening situation necessitating the use of the test article
- Informed consent cannot be obtained 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
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within five working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

Exception from Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergent situations where obtaining prospective informed consent may be waived is provided by 21 CFR 50.24. The research plan must be approved in advance by FDA and the IRB, and publicly disclosed to the community in which the research will be conducted.

These investigations involve human subjects who have a life-threatening medical condition that necessitates urgent intervention (for which available treatments are unproven or unsatisfactory), and who, because of their condition (e.g., traumatic brain injury) cannot provide informed consent. The research must have the prospect of direct benefit to the patient and must involve an investigational product that, to be effective, must be administered before informed consent from the subject or the subject's legally authorized representative can be obtained and in which there is no reasonable way to identify prospectively individuals likely to become eligible for participation.

The regulations at 21 CFR 50.24 and the conforming amendments contained in 21 CFR Parts 56, 312, 314, 601, 812, and 814 provide a narrow exception to the requirement that the investigator obtain informed consent from each subject, or the subject's legally authorized representative, prior to enrollment in emergency research. The regulations also provide additional protections for subjects enrolled in these studies. For example, the regulations require consultation with representatives of and 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. They also require public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study. The regulations also require that an independent data monitoring committee exercise oversight of the clinical investigation.

Treatment IND

The Treatment IND [21 CFR 312.20] is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug may be effective and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

Various FDA regulations and policies also allow certain persons not enrolled in clinical trials to obtain access to investigational drugs:

- A treatment investigational new drug is a treatment protocol that is added to an existing Investigational New Drug Application (IND) that allows physicians to treat qualifying subjects according to the protocol. The IND must also provide additional data on the drug's safety and effectiveness.

- A "single patient use" allows a physician to obtain access to an investigational drug for the treatment of a single patient. Usually, the patient is in a desperate situation and unresponsive to other therapies or is in a situation where no approved or generally recognized treatment is available. Further, there usually is 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 through the sponsor under a treatment protocol. Access may also come 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.

- The Parallel Track policy [57 FR 13250] permits wider access to promising new drugs for AIDS/HIV related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. It provides an administrative system that expands the availability of drugs for treating AIDS/HIV.

There are four requirements that must be met before a treatment IND can be issued:

- The drug is intended to treat a serious or immediately life-threatening disease
- There is no satisfactory alternative treatment available
- The drug is already under investigation, or trials have been completed
- The trial sponsor is actively pursuing marketing approval

Treatment IND studies require prospective IRB approval. A sponsor may apply for a waiver of local IRB review under a treatment IND if it can be shown to be in the best interest of the subjects, and if a satisfactory alternate mechanism for assuring the protection of human subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the informed consent requirement. An IRB may still opt to review a study even if FDA has granted a waiver.

Expanded Access of Investigational Drugs

Investigational products are sometimes used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The procedures that have evolved for an investigational new drug used for these purposes reflect the recognition by the FDA that, when no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval. [21 CFR 312.310, 21 CFR 312.315, 21 CFR 312.320]

Group C Treatment IND

The "Group C" treatment IND was established by agreement between 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 treatment is the primary objective and subjects treated under Group C guidelines are not part of a clinical trial, safety and effectiveness data are collected.

FDA contacts:

For drug products contact: **Division of Drug Information** (301) 796-3400 or (855) 543-3784 Email:druginfo@fda.hhs.gov **Investigational Biological Products** **Office of Communication, Outreach, and Development** (240) 402-8020 or (800)-835-4709 or Email: industry.biologics@fda.hhs.gov	Nights and weekends: **Office of Crisis Management & Emergency Operations Center** (301) 796-8240 or (866) 300-4374

DEFINITIONS

Biological and Drug Products defined as:

- A substance recognized by an official pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.
- Biological products include a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Clinical investigation- defined as an experiment in which a drug (whether approved or unapproved) is administered or dispensed to, or used, and involves one or more human subjects.

Emergency use- defined as the 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.

- Life threatening includes the scope of both life threatening and severely debilitating.

- Life threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life threatening do not require the condition to be immediately life threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

- Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Investigator-Sponsor - an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The requirements applicable to a sponsor-investigator include requirements applicable to an investigator and a sponsor.

Sponsor- may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization that takes responsibility for and initiates a clinical investigation. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor (not a sponsor-investigator) and the employees are investigators.

Also see:

- FDA Information Sheet: "Emergency Use of an Investigational Drug or Biologic: *Guidance for Institutional Review Boards and Clinical Investigators*"
- FDA Information Sheet: "Exception from Informed Consent Requirements for Emergency Research-Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors"
- FDA Information Sheet: "Expanded Access to Investigational Drugs for Treatment Use: Questions and Answers"
- FDA Guidance: "IND Application Procedures: Exemptions from IND Requirements"