I. PURPOSE:

The purpose of this policy is to establish a procedure for reviewing and approving clinical research using investigational or study agents (e.g. drugs or biologics) at Beaumont Health.

II. SCOPE:

This policy applies to investigators, key personnel, Institutional Review Board (IRB) members and staff. The IRB of record for Beaumont research may be the Beaumont IRB or an approved external IRB, in accordance with IRB policy Review by an External Institutional Review Board. Except where noted, the policy requirements apply to all Beaumont research involving investigational or study agents, regardless of a study’s IRB of record.

III. DEFINITIONS:

A. Investigational or Study Agent - Investigational agent refers to any agent which has not received Food and Drug Administration (FDA) approval or which was previously approved and is being evaluated for a new and different indication in humans.

Study agent refers to any agent which is either: 1) FDA approved and is being used under protocol for human research, possibly as a control or outside of the FDA approved labeling; or 2) is not regulated by the FDA (such as vitamins or herbal supplements).

B. Drug - A drug is defined as:
   1. A substance recognized by an official pharmacopoeia or formulary.
   3. A substance (other than food) intended to affect the structure or any function of the body.
   4. A substance intended for use as a component of a medicine but not a device or a component part or accessory of a device.
   5. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (i.e., chemical process versus biological process).

C. Investigational New Drug Application (IND) - An Investigational New Drug Application (IND) is a request from a sponsor (individual, pharmaceutical company, governmental agency, academic institution, private organization, or other organization) for authorization from the FDA to administer an investigational drug or biological product to humans. All clinical evaluations of investigational or study agents, unless exempt, must receive an IND acknowledgement or notice of exemption from the FDA before the study is approved by the IRB and initiated at Beaumont. The IND is assigned a number by the FDA. This number must be provided to the IRB as part of the initial IRB application.

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When research involves the use of an approved agent outside of its FDA-approved indications, the study sponsor must either have an IND or the protocol must meet one of the FDA exemptions from the requirement to have an IND. Exemptions from IND requirements are:

1. **Exemption 1**
   Studies of an FDA-approved agent which is lawfully marketed in the United States, with all of the following conditions being met:
   a. The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling of the agent.
   b. If the agent undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product. The investigation does not involve a route of administration or dosage level or use in a patient population, or other factors which significantly increase the risks (or decrease the acceptability of the risks) associated with the use of the drug product.
   c. The investigation is conducted in compliance with 21.CFR 50.
   d. The investigation is conducted in compliance with 21.CFR 312.7.
   e. The study does not intend to invoke 21 CFR 50.24 (Refer to IRB policy 227 Planned Emergency Research).

2. **Exemption 2**
   A clinical investigation for an in vitro diagnostic biological product which involves one or more of the following medically established diagnostic product or procedures:
   b. Reagent red blood cells.
   c. Anti-human globulin.
   d. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another medically established, diagnostic product or procedure.
   e. The diagnostic test is shipped in compliance with 21 CFR 312.60.

3. **Exemption 3**
   An agent intended solely for tests in vitro or in laboratory research animals.

4. **Exemption 4**
   A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.
   Neither an IND nor IRB review is required for “off-label” use of a marketed drug or biologic as long as such use is strictly for clinical care purposes, and the results are not presented as research. When a study involves off-label use of a drug or biologic, for example to develop new information about the product’s safety or efficacy, or to evaluate a new indication, the FDA requires an IND and IRB approval prior to study initiation. A sponsor may apply for an FDA waiver from all or part of the IND requirements. If specific criteria are met, the FDA will provide a waiver letter.
D. **Commercial IND** - An IND application typically submitted to the FDA by either a corporate entity or one of the institutes of the National Institutes of Health (NIH). The Center for Drug Evaluation and Research (CDER) may designate other INDs as commercial if it is clear the sponsor intends the product to be commercialized at a later date. For a commercial IND, the sponsoring agency is responsible for the overall conduct of the study. Site Principal Investigators (PI) are responsible for the conduct of the study only at their site.

E. **Sponsor-Investigator IND** - An IND application submitted to the FDA by an individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug is being administered or dispensed. An investigator who files an IND is also said to “hold the IND” for the specific study protocol. The physician is referred to as a “sponsor-investigator” and assumes the regulatory responsibilities of both investigators and sponsors, per federal regulations. (Refer to 21 CFR 312 for complete information on sponsor-investigator obligations in accordance with federal regulations.) If a pharmaceutical company will be supplying the drug, but will not itself be submitting the IND, the company is not the sponsor.

F. **Emergency Use IND** - Allows the FDA to authorize use of an experimental drug in an emergency situation which does not allow time for submission of an IND in accordance with 21CFR, Sec. 312.23 or Sec. 312.34. 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 (IRB policy 210 *Single Time Emergency Use*).

G. **Expanded Access** - Expanded Access (sometimes called "compassionate use"), is the use of an investigational drug outside of a clinical trial to treat a patient (or patients) with a serious or immediately life-threatening disease or condition where no comparable or satisfactory alternative treatment options exist.

FDA regulations allow access to investigational drugs for treatment purposes on a case-by-case basis for an individual patient, or for intermediate-size groups of patients with similar treatment needs who otherwise do not qualify to participate in a clinical trial. They also permit expanded access for large groups of patients who do not have other treatment options available, once more is known about the safety and potential effectiveness of a drug from ongoing or completed clinical trials (IRB policy 250 *Compassionate Use and Expanded Access*).

H. **Treatment IND** - A treatment IND application, a type of expanded access, 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 (IRB policy 250 *Compassionate Use and Expanded Access*).
I. Off-Label Use - An FDA approved drug being used for a non-approved indication. The off-label use of a marketed drug for individual patient treatment rather than for research purposes does not require IRB review. However, if the goal of the use is to gain a new indication for the drug, an IND is required and the protocol requires IRB review and approval.

J. Sponsor-Investigator - An individual who both initiates and conducts a clinical trial, alone or with others, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (i.e., it does not include a corporation or an agency).

K. Investigational Drug Service (IDS) - The Investigational Drug Service (IDS) is a service line within the Department of Pharmaceutical Services which manages all investigational and study agents used in the conduct of Beaumont research involving human participants. Located on the Royal Oak campus, the IDS provides administrative oversight for all locations within Beaumont. Certain functions of the IDS (e.g. dispensing) may be delegated to other qualified Beaumont employees not located on the Royal Oak campus (e.g. Beaumont Troy Department of Pharmaceutical Services).

L. Adverse Event - Adverse Events (AEs) are any undesirable or unintended occurrence during participation in the research study, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, emotional response, or disease, whether or not considered related to study participation.

M. An Unexpected Adverse Event is defined as any adverse event occurring in one or more participants enrolled in a research study, in which the nature, severity, or frequency is not consistent with either:

1. The known or foreseeable risk(s) associated with participation in the research described in study-related documents (e.g., the IRB-approved protocol, informed consent and authorization document, investigator brochure (if applicable), other relevant sources of information (product labeling and package inserts)) OR
2. The expected natural progression of any underlying disease, disorder, or condition of the participant(s) experiencing the adverse event and the participant(s) predisposing risk factor profile for the adverse event.

N. Unanticipated Problems Involving Risk to Participants or Others* - PIs must understand the Unanticipated Problem (UP) definition used by the IRB of record for their particular trial and comply with associated reporting requirements of that IRB. The Beaumont IRB defines a UP as:

Any incident, experience or outcome which meets all three (3) of the following criteria:

1. Unexpected (in terms of nature, severity or frequency) given the description in the IRB-approved protocol and informed consent and authorization document and the characteristics of the study population.

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2. Related or possibly related to participation in the research.
3. Suggests the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. A new or increased risk may be defined as one which requires some action such as a modification of the consent process or informing participants.

* “Others,” in the context of this definition and policy, refers to individuals who are themselves not participants but for whom an event may present unanticipated risks. For example, a breach of confidentiality involving inappropriate release of genetic information which occurs during the course of a study represents unanticipated risk to participants and also “others” (in this case, “others” are the blood relatives of participants).

### Unanticipated Problems (UPs) include:

1. An On-Site event (including adverse events, injuries, side effects, problems) which meets all three (3) UP criteria described above.
2. An Off-Site event which the sponsor determines is a UP and has been reported to the appropriate government agency(s).
3. Any accidental or unintentional change to the IRB-approved protocol which involves risks or has the potential to recur.
4. Any change to the research protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
5. Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected detrimental change to the risks or potential benefits of the research.
6. Any breach of confidentiality which may involve risk to participants or others.

Refer to IRB policy [Reporting an Unanticipated Problem Involving Risk to Participants or Others](#)

### IV. POLICY:

In accordance with federal regulations and Beaumont policies, all research projects involving drugs or biologics require review and approval by an IRB. The PI will make the initial assessment as to whether an IND application is required. The IRB will make the final determination whether an IND is required, prior to approving the study.

### V. PROCEDURE:

A. When an IND is required, the IRB will necessitate evidence of an IND prior to study approval or activity, including recruiting, obtaining consent, and screening of participants. An IND goes into effect 30 days after the FDA receives the IND request, unless the sponsor receives earlier notice from the FDA.
B. Regardless of whether a Beaumont study is being reviewed by the Beaumont IRB or an external IRB, an iMedRIS application must be submitted. For studies reviewed by an external IRB, the iMedRIS application is brief and facilitates an administrative review. When a study involves a drug or biologic, the drug section of the application must be completed. The application will be automatically routed to the IDS for review, logistical planning and approval. Refer to Clinical SOP 604 *Investigational and Study Agent Management*. For studies involving investigational and/or FDA-approved drugs or biologics, the IRB application requires:

1. A description of the research to be conducted.
2. Whether the proposed research will be conducted under an IND.
3. The identity of the IND holder.
4. A copy of the IND acknowledgement letter (provided by the FDA to the IND holder).
5. For an investigator initiated trial, if the FDA has not responded within the 30 day period, any email communication with the FDA must be submitted with the IRB application. If the research is exempt from IND requirements, the PI must identify the Exemption Category in the IRB application.
6. If the FDA has granted a waiver from IND requirements, the FDA waiver letter must be included with the IRB application.
7. If the study involves a new indication for the drug or biologic, the PI must describe the planned use of the test article (e.g., new use, altered dose, new route of administration, new participant population, etc.).
8. The Investigator’s Brochure and/or package insert must be included with the IRB submission and the reason for placebo use described, if applicable.
9. A description of the oversight of drug administration, the drug accountability plan, including receipt, storage, dispensing and final disposition and accountability of the drug.

C. PI Responsibilities for Investigational Agents - The PI is responsible for tracking and providing oversight of FDA-regulated drugs and biologics in research. Requirements for use of investigational or study agents in research are as follows:

1. The investigational agent must be used only by the PI or approved sub-investigators under the PIs direct supervision; and
2. The investigational agent must be used only for the approved research indications and under the conditions approved by the FDA and as described in the currently approved protocol; and
3. The PI must not supply the investigational agent to any persons not authorized under the IND; and
4. Informed consent from the participant or the participant’s legally authorized representative must be prospectively obtained, unless waived by the IRB; and
5. Storage must be under lock and key and disposal/return of the investigational drugs must be appropriate, in accordance with the sponsor’s instructions, controlled by the IDS.

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pharmacist and consistent with Clinical SOP 604 *Investigational And Study Agent Management* and other Beaumont policies; and

6. The IDS Pharmacist must maintain complete drug accountability records, including records of receipt, use or disposal, records of dispensing or administering drug to each subject and return. (See Clinical SOP 604 *Investigational and Study Agent Management*.)

D. **Reporting Requirements** - Use of the investigational study agent during research may result in an adverse event (AE). AE’s must be reported to the sponsor according to the protocol. If the AE also meets the IRB of record’s definition of an unanticipated problem (UP), the UP must be reported to the IRB of record, consistent with their policies The IRB of record may be the Beaumont IRB or an approved external IRB. (Refer to IRB Policy *Reporting an Unanticipated Problem Involving Risk to Participants or Others*).

A PI or sponsor who determines an AE presents an unreasonable risk to participants must terminate or suspend the study or any study-specific procedures which present additional risk as soon as possible.

E. **Sponsor-Investigator Responsibilities**: An investigator who files an IND is said to “hold the IND” for the specific study protocol. Investigators who hold an IND (investigator-initiated/investigator-sponsor IND) have responsibilities for reporting AEs to the FDA. The FDA requirements for reporting AE’s are as follows:

1. The sponsor is required to notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug within seven (7) calendar days after the sponsor-investigator’s initial receipt of the information.

2. Within 15 calendar days after the sponsor-investigator’s initial receipt of the information, the sponsor is required to notify the FDA and all participating investigators in a written IND safety report of:
   a. Any adverse experience associated with the use of the drug that is both serious and unexpected; or
   b. Any finding from tests in laboratory animals which suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity.

3. A sponsor-investigator is responsible for promptly reviewing all information relevant to the safety of the drug obtained from any source, either foreign or domestic, including but not limited to information derived from any clinical or epidemiological investigation, animal investigation, reports in the scientific literature, unpublished papers, and reports from foreign regulatory authorities.

4. The sponsor-investigator is responsible for safety reporting to the FDA.

5. The sponsor-investigator is responsible for FDA IND record keeping and submission requirements pertaining to both investigators and sponsors. The sponsor-investigator, as
IND holder, must meet all FDA reporting obligations related to maintaining the IND, including but not limited to protocol amendments, information amendments, IND Safety Reports, and annual reports. (Refer to 21 CFR 312 for complete information on sponsor-investigator obligations in accordance with federal regulations.)

VI. APPLICABLE REGULATIONS AND GUIDELINES:

21 CFR 50 – Protection of Human Subjects
21 CFR 56 – Institutional Review Boards
21 CFR 312 – Investigational New Drug Application
21 CFR 601 – Biologics

VII. REFERENCES TO OTHER APPLICABLE POLICIES:

IRB Policy IRB Initial Review of Research Protocols
Research policy Responsibilities of the Principal Investigator

CORPORATE AUTHORITY:

Beaumont Health (“BH”) as the corporate parent to William Beaumont Hospital, Botsford General Hospital, and Oakwood Healthcare Inc., (“Subsidiary Hospitals”) establishes the standards for all policies related to the clinical, administrative and financial operations of the Subsidiary Hospitals. The Subsidiary Hospitals, which hold all health facility and agency licenses according to Michigan law, are the covered entities and the providers of health care services under the corporate direction of BH. The Subsidiary Hospitals’ workforces are collectively designated as BH workforce throughout BH policies.