Title: **Reporting an Unanticipated Problem Involving Risk to Participants or Others**	*Applicable to: **Beaumont Health**	Effective Date: **01/12/2018**
		Last Periodic Review Date: **01/12/2018**
Policy Owner: **Administrative Director**	Document Type: **Policy**	Functional Area: **IRB and Clinical Research, Research Institute**

***For This Document, Beaumont Health Includes**:
Beaumont Corporate Shared Services
Beaumont Hospital, Dearborn
Beaumont Hospital, Farmington Hills
Beaumont Hospital, Grosse Pointe
Beaumont Hospital, Royal Oak
Beaumont Hospital, Taylor
Beaumont Hospital, Trenton
Beaumont Hospital, Troy
Beaumont Hospital, Wayne
Beaumont Medical Group
Beaumont Pharmacy Solutions
Post Acute Care

I. PURPOSE:

The purpose of this policy is to:

A. Define Unanticipated Problems Involving Risk to Participants or Others, hereafter referred to as Unanticipated Problems (UPs).

B. Ensure principal investigators (PIs) and key personnel understand UPs must be reported to the Institutional Review Board (IRB) of record for the particular study, in accordance with the policies of the respective IRB. The IRB of record may be the Beaumont Health IRB (Beaumont IRB) or an approved external IRB.

C. Establish procedures for reporting and review of UPs when Beaumont IRB serves as IRB of record, including timely reporting of UPs by the PI to the Beaumont IRB and review of reported UPs by the Beaumont IRB.

D. Establish procedures to ensure any IRB of record reports confirmed UPs to the Beaumont Health Institutional Official (IO) for research.

E. Establish administrative procedures by which the Beaumont IO reports UPs to Beaumont administrators and external regulators, when appropriate.

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II. SCOPE:

This policy applies to all human participant research conducted at Beaumont or utilizing Beaumont facilities, patients or staff. This policy represents the minimum reporting standards and may be superseded by federal regulations or, in some cases, an external IRB of record.

III. RESPONSIBILITY:

Federal regulations require institutions engaged in human participant research to have written procedures for ensuring prompt reporting by investigators of UPs to the sponsor and IRB of record and ensuring prompt reporting by the IO to appropriate institutional officials, OHRP and other regulatory agencies, such as the FDA when appropriate, and any supporting department or agency head. The PI bears responsibility for identifying **On-Site UPs** and assuring provision of associated clinical care to safeguard the participants' well-being and rights. The PI also bears responsibility for reporting UPs (both On-Site and Off-Site) to the sponsor and the IRB of record, in accordance with the IRBs policies and for proposing any changes required to ensure protection of human participants**. The IRB of record may be Beaumont IRB or an approved external IRB.** The IRB of record is responsible for conducting a meaningful review of the PI's report and making a determination whether the event meets criteria as an UP, if actions by the PI are adequate and/or if imposing further actions to protect human participants, if necessary. In addition, the IRB of record is responsible for reporting all On-Site UPs to the Beaumont IO. The Beaumont IO will report all onsite UPs to the Sr. Vice President, Chief Quality and Safety Officer. The IO bears responsibility for promptly reporting all On-Site UPs to OHRP and other regulatory agencies, such as the FDA when appropriate, and assuring appropriate notification of funding agencies.

IV. REPORTING UPs WHEN BEAUMONT IS IRB OF RECORD:

This section of the policy applies when Beaumont IRB is IRB of record. When an external IRB serves as IRB of record, consult policies for the external IRB in question.

A. **Beaumont IRB Definitions - Unanticipated Problems Involving Risk to Participants or Others* (UPs)** include 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.
   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 not themselves participants but for whom an event may present unanticipated risks. For example, if a breach of confidentiality involving inappropriate release of genetic information occurs during the course of a study, this represents unanticipated risk to participants and also "others" (in this case, "others" are the blood relatives of participants).

B. Unanticipated Problems (UPs) include:
   1. An **On-Site** event (including adverse events, injuries, side effects, deaths or other 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 change to the risks or potential benefits of the research.
   6. Any breach of confidentiality which may involve risk to participants or others.
   7. Any participant complaint which identifies an unanticipated risk and is determined by the PI to meet the definition of UP.
   8. Any other related or possibly related event which the PI believes constitutes an unanticipated risk.

C. **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.*

D. 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.

E. A **Serious Adverse Event (SAE)** is defined as any untoward medical occurrence which:
   1. Results in death,
   2. Is life threatening - which refers to an event in which the patient was at risk of death at the time of the event, not that the event would have been life threatening had it been more serious,
   3. Requires inpatient hospitalization or prolongation of existing hospitalization,
   4. Results in persistent or significant disability/incapacity, or
   5. Results in a congenital anomaly/birth defect.

F. **Determination of Event Causality:** The relatedness of each event must be determined and documented by the PI in the study records. When the PI deems the event is **related,** this means there is reasonable possibility the event may have been caused as a result of participation in the research. The IRB interprets "reasonable possibility" to mean "more likely than not." Similarly, "possibly related" means "more likely related than unrelated."

G. **Unanticipated Adverse Device Effects:** Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if the effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IRB application.

H. **On-Site (Internal) UPs:** For purposes of this policy, On-Site UP's are events which meet the definition above and involve Beaumont participants enrolled in a research study for which Beaumont IRB is the IRB of record. This includes events which occur at sites for which Beaumont serves as the Coordinating Center, as the Coordinating Center may be responsible for reporting events to the regulatory authorities and/or sponsor as well as communicating safety information to participating sites.

I. **Off-Site (External) UPs** are events which occur in multi-center trials (when the Beaumont IRB is acting as the IRB or record for the study at Beaumont), involve participants at non-Beaumont sites and have been determined by the sponsor to constitute UPs. When participating in multi-center clinical trials, PIs may receive "Off-Site reports," (e.g., MedWatch) which are sponsor reports of events occurring at other sites for the same trial, or different trials using the same test article. The PI should read these reports and retain them in

their investigator file. The sponsor is responsible for analyzing these events and determining which constitute UPs. Once the sponsor determines an event constitutes a UP, the PI should report these to the Beaumont IRB as an Off-Site UP.

J. **Investigational Device Exemption (IDE):** An FDA approved investigational device exemption (IDE) permits a device to be shipped lawfully for the purpose of conducting investigations of the device.

K. **Investigational New Drug (IND):** An FDA approved investigational new drug (IND) or biologic used in a clinical investigation. The term also includes a biological product used in vitro for diagnostic purposes.

L. **Sponsor-Investigator:** An individual who both *initiates* and *conducts* a clinical investigation, alone or with others, and under whose immediate direction the investigation is administered or dispensed (i.e., the investigational drug or device is administered, dispensed or used). The term does not include any person other than an individual. The regulatory obligations of a sponsor-investigator include both those of an investigator and a sponsor. (Refer to 21 CFR 312 for complete information on sponsor-investigator obligations.)

M. **Beaumont IRB Reporting Criteria - Beaumont IRB Reporting Requirements for Both Sponsored and Investigator-Initiated Studies:** The PI must report On-Site and Off-Site UPs to the Beaumont IRB in the manners described below. Documentation of the PI's assessment of On-Site event reportability must appear in the study records.

N. **On-Site UPs:** An On-Site UP which occurs during the study or within thirty (30) days of study closure (or longer if specified by the protocol) must be reported to the Beaumont IRB within **seven (7) business days** of the PI becoming aware of the event. In the report, the PI must include proposed actions necessary to protect the well-being and rights of participants and others. For example, the PI may propose changes to the inclusion and exclusion criteria and proceed to obtain Beaumont IRB and sponsor approval, or the PI may place the research on Administrative Hold (refer to Beaumont IRB policy 254 *Administrative Holds, Suspensions and Terminations*). If an event does not meet the reporting requirements as listed above, submission of an UP form to the IRB is **not** required. **When using an external IRB, and a UP occurs internally at Beaumont, the external IRB of records' policy on UP reporting must be followed.**

O. **Off-Site UPs:** The PI is responsible for reviewing Off-Site events reported by the sponsor. Off-site events **which sponsors determine meet the definition of UP must be reported to the IRB within seven (7) business days** of PI becoming aware of the sponsor determination.

The PI reports risk mitigation measures initiated by the sponsor (or by the PI) to the IRB; these measures are reviewed for adequacy by the IRB. Additionally, the PI is responsible for confirming the sponsor (or investigator at another institution) has reported the event to OHRP or other regulatory agencies, such as the FDA, when required. Off-Site events which the sponsor does not designate as UPs **are not** reported to the IRB, but must be maintained in the study file. All documents related to Off-Site events (e.g., supporting source documents, MedWatch reports) must be reviewed by the PI and maintained in the PI's study file/regulatory binder, including reports of events which do not meet IRB reporting criteria.

P. **Sponsor Reporting Requirements**: Reporting requirements by the PI to a study sponsor or funding body may differ significantly from the IRB reporting requirements. The PI must satisfy these reporting requirements as outlined in the protocol, clinical trial agreement and in accordance with the Federal regulations which apply to the investigational drug or device.

Q. **Investigator-Initiated Research Reporting (IIR) Requirements**: A sponsor-investigator conducting a study under an IND or IDE assumes additional responsibilities. These responsibilities include reporting safety information directly to the FDA, and to both the FDA and investigators at other sites, for multi-center trials, in accordance with 21 CFR 312.32. When an FDA-regulated IIR study involves a clinical research organization (CRO), such as Beaumont Research Coordinating Center (BRCC), the sponsor-investigator (PI) may transfer, in writing, certain trial-related duties/functions to the CRO, including safety reporting , but the ultimate responsibility resides with the PI. The FDA requirements for reporting potential serious risks include:

1. Notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of an investigational drug within **seven (7) calendar** days of the sponsor-investigator's initial knowledge of the information.
2. Inform the FDA and all participating investigators, within **fifteen (15) calendar** days following initial knowledge of the information, via a written IND safety report of:
   a. Any adverse experience associated with the use of the drug which 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. Within **ten (10) business days** of learning of an unanticipated adverse device effect, conduct an evaluation and report findings to the FDA and all participating investigators. (Refer to 21 CFR 312 and 21 CFR 812 for complete information on sponsor-investigator obligations.)

R. **Other Required BH IRB Reporting**

1. The reporting timelines (described above) must be observed, even if the information contained in the UP report is incomplete. The initial UP On-Site report must be submitted within seven (7) business days. When further information is available, a follow-up report must be filed. If the PI is unavailable (e.g., out of town) a sub-investigator must assess the event and report the UP per this policy using Study Correspondence in iMedRIS. The PI will review and submit a formal UP report to the IRB within seven business days of his/her return.
2. Summary Information: The PI may receive summary UP information, such as a Data Safety Monitoring Board (DSMB) report (not individual reports) from the sponsor, CRO or DSMB. Such summary reports, should be submitted to the IRB within seven (7) days of PI receipt. Summary UP Reports the PI receives from the sponsor after the study has been closed with the IRB will be accepted if the new information being reported effects health or well-being of previously enrolled participants. The IRB may determine additional action is required (e.g., notification of participants by the PI).
3. All documents related to both On-Site and Off-Site events (e.g., supporting source documents, MedWatch reports) must be reviewed by the PI and maintained in the PI's study file/regulatory binder, including reports of events which do not meet IRB reporting criteria. The PI's assessment of each on site event (including severity, causality and relatedness) must be clearly documented and reflect the date of PI assessment.
4. Non-compliance with these reporting requirements will be reviewed at a convened IRB meeting and adjudicated on a case-by-case basis. The IRB Chair or designee will notify the IO. The IRB Chair and/or IO may take appropriate action, including but not limited to halting the research.
5. If the PI determines an event is not an UP, but the sponsor or monitoring entity subsequently determines the event does in fact represent an UP (e.g., due to an unexpected higher frequency of the event), the sponsor or monitoring entity will report this determination to the PI and the PI must promptly report the event to the IRB.
6. Any proposed changes to the research protocol in response to an UP must be approved by the sponsor and the IRB prior to implementation, except when necessary to eliminate apparent immediate hazard to participants. If the PI determines a change is necessary prior to approval to protect the life or physical well-being of a participant and eliminate immediate hazard in an emergency, a report must be provided to the IRB and sponsor as soon as possible, but no later than five (5) business days after the emergency occurred.
7. When an On-Site UP meets the IRB reporting criteria and also involves gene therapy research, the PI must report to the sponsor, the IRB and Beaumont Health Institutional Biosafety Committee (IBC) as soon as possible, but not later than seven (7) business days, in accordance with IBC standard operating procedures. The IBC will assist the PI in

reporting the event to the National Institute of Health (NIH) as appropriate. For information on IBC reporting standards, PIs may contact the IBC Chair.

S. **Beaumont IRB Review of Unanticipated Problems -**The UP Reviewer (IRB Chair or designee) will triage submitted onsite UP reports to determine whether reported problems qualify as UPs. The IRB Chair may suspend the research immediately, pending review by the full committee, if it is believed continuing the research places participants or others at immediate risk of new or increased harm than was previously known. On-Site (submitted UP reports which qualify as UPs, per the UP Reviewer's determination) and Off-Site reports (which qualify as UPs, per the sponsor) are verbally presented to the fully convened IRB by the IRB Chair or UP Reviewer. The UP Reviewer may contact the PI or others for additional information to evaluate if the action proposed to mitigate risk is adequate and/or if additional action is required to protect participants. All reported UPs meeting the definition of a UP are also placed on the IRB meeting agenda including the IRB project number, project title, PI name, Chair or designee as reviewer, reason event classified as UP, and detailed description of the event. The UP report and supporting documentation are available to IRB members in iMedRIS. The IRB actions may include:

1. Suspend or terminate the research (refer to IRB policy 254 *Administrative Holds, Suspension and Terminations*).
2. Modification of information disclosed during the consent process.
3. Requiring current participants to re-consent to participation.
4. Monitoring of the consent process.
5. Referral to other organizational entities, such as the Office of Quality and Safety. UPs suggestive of potential non-compliance are promptly reported to the IO and the Research Compliance Coordinator, consistent with IRB policy, *Contacts, Complaints, Allegations of Non-Compliance and Confirmed Non-Compliance in Clinical Research*.
6. Request further clarification from the PI, sponsor, study coordinating center, or DSMB.
7. Require changes to the protocol.
8. Require modification of inclusion or exclusion criteria to mitigate the newly identified risks.
9. Require additional procedures for monitoring participants.
10. Require a change in the continuing review process.
11. Require additional monitoring by the IRB or the Research Institute Clinical Research Quality Improvement Program (CRQIP).
12. Require notification of regulatory agencies.

The IRB will confirm the occurrence meets the definition of UP, discuss and record the presence of the IRB members. If there are required changes to the protocol, the IRB will

request the changes and communicate with the PI of the study. All UP discussion will be recorded in the meeting minutes. The PI will be informed with an outcome letter, in a timely manner, of any action taken and/or required by the IRB. Additionally, if the IRB Chair or convened IRB determines a more in-depth evaluation of the UP is required, the IRB Chair may request the Sr. Vice President, Chief quality and Safety Officer to initiate a formal peer-reviewed evaluation. Confirmed UPs are reported to the IO, who reports them to OHRP.

V. ADMINISTRATIVE REPORTING REQUIREMENTS:

A. **Administrative reporting requirements apply to all onsite UPs, regardless of which IRB is serving as IRB of record (Beaumont IRB or an external IRB).** IRBs of record overseeing Beaumont research, including Beaumont IRB and approved external IRBs, are required to report confirmed On-Site UPs to the IO. For studies overseen by Beaumont IRB, the IRB Chair or IRB Manager will prepare a report for the IO within fourteen (14) business days of the IRB meeting where it was determined the event constituted an UP. The report will include:

1. The title of the research project
2. The name of the PI
3. The IRB protocol number
4. A description of the event
5. An explanation indicating why the event is reportable
6. Actions being taken to address the event: if the action is complete, this information is provided in the initial report; if further action is forthcoming, the immediate action is reported, including a statement that a final report will be sent upon implementation of all corrective action(s), including a target date for the report.

When an external IRB serves as IRB of record overseeing Beaumont research, the external IRB is required to promptly report On-Site UPs to the Beaumont IO.

B. Within fourteen (14) business days of receiving the IRB's report, the IO notifies the Sr. Vice President, Chief quality and Safety Officer and appropriate federal regulatory agencies, if necessary. The IO or designee completes a final report of the event and the corrective actions taken and submits the report to the applicable external regulatory body, as noted below. The report will include the following information, minimally:

1. The name of the institution conducting the research
2. The title of the research project
3. The name of the PI
4. The IRB protocol number
5. A description of the event

6. An explanation indicating why the event is reportable
7. Actions being taken to address the condition: if the action is complete, this information is provided in the initial report; if further action is forthcoming, the immediate action is reported including a statement that a final report will be sent upon implementation of all corrective action(s), including a target date for the report.

The IO or designee submits the report to:

1. The IRB of record (Beaumont IRB or the approved external IRB). When Beaumont IRB is IRB of record, the report is added to the agenda of the next meeting.
2. The PI and PI's department Chair
3. The FDA if the research is accountable to FDA regulation
4. OHRP
5. Department of Defense: UPs for any DoD-supported research must be promptly (within thirty (30 days) reported to the DoD human research protection officer.
6. Any other federal agency with jurisdiction over the research study if the agency requires reporting separate from reporting to the OHRP
7. Study funding agency or sponsor, if not previously notified
8. Others as deemed appropriate by the IO.

VI. POLICIES AND PROCEDURES:

Research Policy 110 *Biosafety Committee Operations*
IRB Policy *Contacts, Complaints, Allegations of Non-Compliance and Confirmed Non-Compliance in Clinical Research*
IRB Policy 205 *Continuing Review and Renewal of a Protocol*
IRB Policy *Informed Consent and Authorization in Research*
IRB Policy 223 *Investigational Device Research*
IRB Policy 253 *Investigational New Drug Research*
IRB Policy 254 *Administrative Holds, Suspensions and Terminations*

VII. REGULATORY REFERENCES:

Title 21 CFR 312.; 21 CFR 812: Title 45 CFR 46.103
ICH 4.11
FDA Information Sheet: Guidance for Institutional Review Boards and
Clinical Investigators "Process for Dealing with Reports of Adverse Reactions and Unexpected Events"

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OHRP and HHS "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Participants or Others and Adverse Events." January 15, 2007
National Institute of Health (NIH) Guidelines for Use of Recombinant DNA

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 as BH workforce throughout BH policies.