Title: **Protocol Deviations**	*Applicable to: **Beaumont Health**	Effective Date: **03/19/2018**
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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 define protocol deviations and the subsequent actions required by the Principal Investigator (PI) once a protocol deviation occurs or is discovered.

II. SCOPE:

This policy applies to investigators and key personnel when the Beaumont Health (Beaumont) Institutional Review Board (IRB) serves as IRB of record for a study; this policy applies to its members and staff.

III. BACKGROUND:

The Beaumont IRB or the external IRB serves as the IRB of record for all human participant research conducted at Beaumont. **The Beaumont Health (Beaumont) IRB serves as the primary Institutional Review Board for human participant research conducted at Beaumont (for information about the use of external IRB's, see policy *Review by an External Institutional Review Board*).** In accordance with federal regulations, IRB review and approval is required to protect the rights and welfare of human participants. The IRB of record will review, assess and determine any course of action necessary with regard to protocol deviations.

IV. RESPONSIBILITY:

The IRB of record and the PI are jointly responsible for protecting the safety of human participants enrolled in research studies. The IRB of record is responsible for the continuous assessment of risk versus benefit and reviewing protocol deviations, taking appropriate action to protect human participants and ensuring compliance with research policies and regulations. The PI bears responsibility for all aspects of protocol deviation reporting including developing an appropriate action plan to avoid future similar deviations. All PI's and Key Personnel, must know and follow the IRB of records policies. Key personnel bear the responsibility of communicating with the PI when they become aware a protocol deviation has occurred. The PI is required to promptly notify the IRB of record of any event which meets the criteria of a protocol deviation per the policy for the IRB of Record.

V. POLICY:

When Beaumont IRB is IRB of record for a study, all protocol deviations, regardless of their nature, must be captured and reported to the Beaumont IRB and, for externally sponsored research, to the study sponsor. When an external IRB is IRB of record, protocol deviations must be reported to the external IRB in compliance with that IRB's policies, and to the study sponsor. PIs and staff working with an external IRB must be knowledgeable about the IRB of record policies. **The remainder of this policy pertains to studies overseen by the Beaumont IRB.**

A. **Deviation from Investigational Plan Made to Protect the Life or Physical Well-being of a Participant in an Emergency -** Deviations from the protocol require prospective IRB and sponsor approval. If the PI determines a deviation 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 working days** after the emergency occurred.

B. **Other Deviations**
   1. **IRB Reporting:**
      a. **Major** protocol deviations (as defined below) must be *submitted to the IRB within seven calendar (7) days of the PI's* knowledge of the occurrence, using the Protocol Deviation Report Form in iMedRIS.
      b. **Minor** protocol deviations (as defined below) are not reported at the time of occurrence (unless required by the sponsor). A cumulative log of **Minor** protocol deviations, called the *Minor Protocol Deviation Report Form* must be maintained and submitted to the IRB with the *Progress Report* at the time of continuing review. The

Minor Protocol Deviation Report Form is available in iMedRIS under My Assistant – Operating Procedures and on the IRB website.

2. **Sponsor Reporting:**
   All protocol deviations must be reported to the study sponsor, when a study sponsor exists. A sponsor may provide instructions for capturing and reporting all protocol deviations, such as specific forms. When sponsor's instructions **either:** 1) are not outlined in the protocol or otherwise provided by the sponsor, **or** 2) are less stringent than described below, the PI will report:
   a. **Major** protocol deviations to the sponsor within **seven (7) calendar days** of PI's knowledge of occurrence. If the sponsor has not provided alternative reporting methods, the PI may provide the sponsor with the IRB *Protocol Deviation Report* from iMedRIS.
   b. **Minor** protocol deviations to the sponsor at time of continuing review. If the sponsor has not provided alternative reporting methods, the PI may provide the sponsor with the IRB *Minor Protocol Deviation Report Form.*

If the study has no sponsor (i.e., investigator-initiated research), sponsor reporting is not required. However, when investigator initiated research is overseen by the FDA, the PI must follow FDA direction regarding protocol deviation reporting.

VI. DEFINITIONS:

A. **Informed Consent and Authorization Document (ICAD) -** The ICAD is a document describing the study (including risks and benefits) in lay terminology which is used to inform a participant, or their Legally Authorized Representative (LAR) when appropriate, of all aspects of the research relevant to the participant's decision to participate. The ICAD documents the participant's voluntary willingness to participate in the research project and to allow use of their protected health information.

B. **Substantive Action -** Any action required to minimize or prevent an adverse physical or psychological risk or outcome in a study participant, which requires follow-up treatment or monitoring and is greater than minimal risk.

C. **Protocol Deviation** - A protocol deviation is any inconsistency between the IRB-approved protocol and the actual research activities conducted. Protocol deviations may be **Major** or **Minor**.

D. **Major Protocol Deviation**
   1. **Major protocol deviations** include those which:

a. Result in or require a **substantive action to be taken** to prevent harm to the participant or others.
b. **Harm** or pose a significant **risk of harm** to the research participant.
c. Result in an Unanticipated Problem. When a Major protocol deviation also results in an Unanticipated Problem, the IRB *Unanticipated Problem Form* must be submitted in addition to the *Protocol Deviation Report Form* (see IRB Policy *Reporting an Unanticipated Problem Involving Risk to Participants or Others*).
d. Damage the scientific integrity of study data.
e. Involve willful or knowing misconduct on the part of an investigator or key personnel.
f. Involve serious or continuing noncompliance with federal, state, or local research regulations (see Research Policy *Contacts, Complaints, Allegations of Non-Compliance and Confirmed Non-Compliance in Clinical Research*).
g. Involve participant **eligibility errors** regardless of whether the deviation impacts participant safety, increases risk, or results in an Unanticipated Problem.
h. Involve **test article errors** (drug, device or biologic) such as dosing errors, regardless of whether the deviation impacts participant safety, increases risk, or results in an Unanticipated Problem.
i. Involve any **breach of confidentiality** which violates the Health Insurance Portability and Accountability Act (HIPAA).
j. Involve **Major Consent Errors** (as defined below) regardless of whether the error impacts participant safety, increases risk, or results in an Unanticipated Problem.

2. Examples of **Major protocol deviations** include but are not limited to:
   a. Participant enrollment prior to IRB approval, during a lapse in approval, or during the period a study has been placed on hold.
   b. Enrollment of a participant who did not meet inclusion criteria or who met exclusion criteria.
   c. Performance of a study procedure not approved by the IRB.
   d. Failure to report Unanticipated Problems to the IRB and/or sponsor.
   e. Miscalculation of a medication dose or randomization error resulting in the participant receiving more or less drug than the protocol requires.
   f. Study visit missed or conducted late (outside the protocol-required timeframe) which potentially affects participant safety, health or rights.
   g. Study procedure (e.g., laboratory test) not performed, which in the opinion of the PI or IRB, may affect participant safety.

3. **Major Consent Errors are considered to be protocol deviations** and include but are not limited to:

a. The participant did not sign the study ICAD.
b. The participant did not sign the ICAD before the first research procedure was initiated.
c. The wrong version of the ICAD was used.
d. The participant signed the ICAD for the wrong study.
e. The participant or consent provider did not sign **and** date the ICAD.
f. The consent provider was not authorized by the IRB to obtain consent.
g. The signature of the participant on the ICAD was not witnessed.
h. The LAR signed the ICAD for the participant and it cannot be determined why (i.e., no evidence of cognitive impairment or critical illness in medical chart or research record).
i. A non-English speaking participant signed the English language ICAD without the use of a translator or consent was obtained without a bilingual witness present for the consent procedure and signature of the ICAD.
j. A non-English speaking participant did not sign a translated ICAD or the short form consent prior to having the English language ICAD verbally translated in the participant's native language.
k. The participant belongs to a vulnerable population (i.e., illiterate or visually impaired, to the degree in which the participant is unable to read the ICAD) and was consented without a witness to the entire consent process which are special provisions required per policy.
l. Child assent or assent of a cognitively impaired participant was not obtained or documentation of this process was not completed as required by the IRB Application or policy.
m. The participant was concurrently consented to more than one research study when concurrent enrollment is prohibited by either study protocol, or when concurrent enrollment could affect participant safety.
n. The consent process was not documented with a note in the participant's case history (i.e., medical or research record).
o. A significant acknowledgement field on the ICAD (i.e., authorizing sample storage for future use or providing information about reproductive status) was not completed.
p. A copy of the signed ICAD was not provided to the participant or LAR, as applicable.
q. Someone other than the participant completed fields (i.e., date and time of signature) on his/her behalf.

E. **Minor Protocol Deviation**

1. A **Minor protocol deviation** includes **all** of the following characteristics and does not meet criteria for a Major deviation:
   a. No affect on participant safety or increased risk to participant; and

b. No significant affect on the value of the data collected; and
c. Did not result from willful or knowing misconduct on the part of the investigator(s) or key personnel; and
d. Did not result in or require any substantive action to be taken; and
e. Did not result in any change to the participant's condition or status (i.e., did not affect participant's participation in any way, result in a change to the participant's emotional or clinical condition, cause an unanticipated event, or require a change in the clinical care of the participant).

2. Examples of **Minor protocol deviations** include but are not limited to:
   a. A portion of the protocol was not followed, completed or was omitted (e.g., performance of a laboratory test) which did not affect the rights, health or safety of participants.
   b. A study visit was missed or conducted late (outside of the protocol-mandated timeframe) which did not affect the rights, health or safety of participant.
   c. The participant failed to return study medication(s) and the rights, health or safety of participants was not affected.

VII. PROCEDURE:

A. **Major Protocol Deviations** - All **Major** protocol deviations must be reported to the IRB via a *Protocol Deviation Report* in iMedRIS, within **seven calendar (7) days** of the PI's knowledge of the occurrence. The report must contain a concise description of the deviation, the date of the deviation, and a plan for preventing future similar deviations. In addition, an *Unanticipated Problem Form* must be submitted to the IRB if the deviation resulted in an Unanticipated Problem. The reporting timelines must be observed, even if the information contained in the report is incomplete. A follow-up report must be filed as information becomes available.
   1. **If the PI is unavailable** (i.e., out of town) and cannot assess the protocol deviation, a sub-investigator should make the determination as to whether the event should be reported as a Major protocol deviation. The PI must review the report upon his/her return and submit a memo to the IRB within seven (7) calendar days, concurring with the reported deviation or explaining his/her difference of opinion with the report.
   2. A summary of the deviation and any action taken by the PI will be included in the agenda of the next scheduled IRB meeting. A copy of the *Protocol Deviation Report Form* will be retained in the IRB study file. The IRB will notify the PI in writing of the IRB meeting outcome. The IRB may determine the action plan is sufficient and acceptable as

submitted, may determine additional information is required, or may require additional actions.

3. Major protocol deviations may qualify as episodes of non-compliance. Those suggestive of potential non-compliance are promptly reported to the Institutional Official, the IRB, and the Research Compliance Coordinator, consistent with IRB Policy, *Contacts, Complaints, Allegations of Non-Compliance and Confirmed Non-Compliance in Clinical Research*. Additionally, major protocol deviations may qualify as Unanticipated Problems Involving Risk to Participants and Others (UPs). Those the PI believes qualify as UPs must be reported to the IRB, consistent with IRB Policy *Reporting an Unanticipated Problem Involving Risk to Participants or Others*.

B. **Minor Protocol Deviations - Minor** protocol deviations are not immediately reported to the IRB unless required by the sponsor. **Minor** protocol deviations are added to the *Minor Protocol Deviation Report Form* and reported to the IRB at the time of continuing review.

C. **Emergency Action by the IRB Chair -** In the event the IRB Chair determines the protocol deviation results in substantial risk to participants, confidentiality, or the integrity of the study, the Chair may order:
   1. Suspension of IRB approval (defined as a temporary halt in IRB approval of some or all research activities)

D. Reporting a Breach of Confidentiality - If a breach of confidentiality occurs the IRB will review the circumstances and take corrective action as necessary. Additionally, the IRB will inform the Beaumont Health Privacy Officer, who may also institute corrective action.

E. **Reporting to Outside Agencies** - When protocol approval is suspended or terminated due to protocol deviations involving increased risk(s) to participants or for other reasons, the Institutional Official will report this action to the applicable Federal funding agencies, department heads and if required, to the Office for Human Research Protections (OHRP) per IRB Policy 254 *Administrative Holds, Suspensions and Terminations.*

F. **Informed Consent Audit Program -** All executed ICADs are audited by a clinical research manager (CRM) or designated consent auditor within twenty-four hours of execution, regardless of the IRB of record (i.e. BH IRB or an approved external IRB). Major consent errors, regardless of whether they are considered protocol deviations by the IRB of record, are identified and recorded using Crossbreak, the electronic consent audit tool. When the Beaumont IRB is the IRB of record, major consent errors are reported as major protocol deviations to the Beaumont IRB. Additionally, minor consent errors are captured in Crossbreak. Minor consent errors do not considered minor protocol deviations and are not

reportable to the IRB. For more information, refer Research Policy 502, *Consent Audit Process* (in development).

VIII. APPLICABLE REGULATIONS:

21 CFR 812.140
21 CFR 812.150
45 CFR 46.103

IX. REFERENCES TO OTHER APPLICABLE POLICIES:

RI Policy 113 *Clinical Research Quality and Process Improvement Program*
RI Policy *Contacts, Complaints, Allegations of Non-Compliance and Confirmed Non-Compliance in Clinical Research*
IRB Policy *Reporting an Unanticipated Problem Involving Risk to Participants or Others*
IRB Policy *Informed Consent and Authorization in Research*
IRB Policy 211 *Enrolling Non-English Speaking Study Subjects*
IRB Policy *Continuing Review and Renewal of a Protocol*
IRB Policy 254 *Administrative Holds, Suspensions and Termination*
IRB Policy *Review by an External Institutional Review Board*
IRB Policy *Amendment Requests to the IRB Approved Studies*

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.