Title: **Continuing Review and Renewal of a Protocol**	*Applicable to: **Beaumont Health**	Effective Date: **03/16/2018**
		Last Periodic Review Date: **03/16/2018**
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 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*). The purpose of this policy is to ensure the rights and welfare of human participants participating in research at Beaumont Health are protected. It is the responsibility of the Institutional Review Board (IRB) to conduct continuing review of ongoing research.

II. POLICY:

The Health and Human Services (HHS) and Food and Drug Administration (FDA) regulations for the protection of human participants require institutions to have written procedures the IRB will follow regarding:

A. The conduct of continuing review of research covered by policies at intervals appropriate to the degree of risk, but not less than once per year, and notifying investigators and the institution in writing of its decisions to approve or disapprove the proposed research activity, or if modifications are required to secure IRB approval of the research activity, and

B. Except when an expedited review procedure is used (IRB Policy *Expedited Review of Research*), review proposed research at convened meetings with a majority of members present, including at least one whose primary concerns are in nonscientific areas.

The regulations state continuing review by the convened IRB must be "substantive and meaningful," with votes recorded for each study. HHS regulations set forth criteria which must be satisfied for the IRB to approve the research. These HHS criteria are:

1. Risks to participants are minimized;
2. Risks to participants are reasonable in relation to anticipated benefits;
3. Selection of participants is equitable;
4. Informed consent process is adequate and appropriately documented;
5. Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants;
6. Where appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data; and
7. Appropriate safeguards have been included to protect vulnerable participants. The IRB is required to ensure these criteria are satisfied at the times of initial review and continuing review.

III. CONTINUING REVIEW PROCESS TIMELINES:

Continuing review requests (Progress Reports) for IRB-approved protocols should be submitted to the IRB at least six (6) weeks prior to the approval expiration date. The principal investigator (PI) is responsible for the Progress Report being submitted to the IRB office in time to allow for processing and review prior to the expiration date (i.e., submitted by the IRB meeting submission deadline). The date is noted and highlighted in the initial IRB approval letter and in the current IRB continuation approval letter. The IRB will send the PI a renewal reminder (*Notice of Impending Expiration)* several weeks prior to the date of expiration.

IV. EXPIRATION OF IRB APPROVAL:

A. IRB approval expires at 11:59 p.m. on the stated expiration date. The continuation of research after expiration of IRB approval is a violation of the HHS and FDA regulations. If a Progress Report cannot be reviewed and approved prior to the expiration of IRB approval, the project no longer has IRB approval, and all research activities must stop. No new participants may be enrolled and no data may be collected. Appropriate clinical care should be provided if stopping research activities would place these participants at increased risk of harm.

B. If the IRB believes previously enrolled participants must continue use of the study article or follow up care during a period of expiration, due to an over-riding safety concern or ethical issue, the IRB may permit continuation of those activities for a brief time required to complete the review process. Data collected during this time may not be used for the study. The IRB will

determine the course of action to be taken when a study lapses. See "Full Board Continuing Renewal" in this policy for a full explanation.

V. FINAL CLOSURE AFTER A PERIOD OF STUDY EXPIRATION:

A. If the period of expiration reaches sixty (60) days, the protocol will be administratively closed. Once closed, a project will require resubmission to the IRB as an entirely new project, if the PI wishes to conduct this research with human participants.

B. In addition to stopping all research activities, any participants currently participating must be notified of the study closure for a greater than minimal risk study. Procedures for withdrawal of enrolled participants should consider the rights and welfare of participants. If follow-up of participants for safety reasons is permitted or required by the IRB, the participants should be informed and any adverse events/outcomes should be reported to the IRB and study sponsor.

VI. PROGRESS REPORT SUBMISSION AND REVIEW:

A. Routine continuing review will include IRB review of a Progress Report completed according to IRB policy and submitted through the electronic submission system, iMedRIS, by the PI. The PI is responsible for the accurate completion of the Progress Report.

B. Upon receipt of the required documents (e.g., completed Progress Report, currently approved clean and unstamped copy of the consent and authorization document, assent form and/or an Information Sheet [if applicable], approved advertisements, etc.), the documents will be screened by IRB staff and logged into the database. The Progress Report and the study will be assessed by the IRB staff to determine the level of IRB review required. Continuing reviews requiring full board IRB review will be placed on the agenda of the next scheduled IRB meeting.

C. Special attention will be paid to determining whether new information or unanticipated risks were discovered since the previous review. Any significant new findings which may relate to the participants' willingness to continue participation must be provided to the participants in accordance with HHS and FDA regulations.

VII. FREQUENCY OF REVIEW:

A. The IRB is required to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. The IRB must determine the frequency and extent of continuing review for each protocol is adequate to ensure the continued protection

of the rights and welfare of research participants. The factors considered in setting the frequency of review may include:

1. Nature of the study;
2. Degree of risk involved; and
3. Vulnerability of the study participant population.

B. The specified frequency of review is primarily based upon the probability and magnitude of anticipated risks to participants. If serious new risks are identified at the time of continuing review, the IRB may increase the frequency of review. Criteria employed for assigning continuing reviews more frequently than on an annual basis are:

1. Changes to the medical conditions of participants;
2. Changes in the qualifications and experience of the PI and/or key personnel;
3. Changes in the nature and frequency of adverse events and/or unanticipated problems observed in similar research at this and other facilities; and
4. Vulnerability of the study population.

VIII. LEVEL OF IRB REVIEW:

A. The purpose of the continuing review is to review the progress of the entire study. Continuing review is conducted by the full IRB unless the protocol meets criteria for expedited review. Studies initially reviewed under expedited review criteria, will typically undergo expedited continuing review. In the event the IRB determines, at the time of continuing review, a previously expedited review study now meets greater than minimal risk criteria, the study will be submitted to the IRB full board for determination. Use of the Continuing Review checklist guides this determination. For continuing review of research, the IRB members determine:

1. Whether the protocol needs verification from sources other than the researchers that no material changes have occurred since previous IRB review.
2. The current consent document is still accurate and complete.
3. Any significant new findings since the last review process which could possibly relate to participants' willingness to continue participation will be provided to participants.

IX. EXPEDITED REVIEW PROCEDURES FOR CONTINUING REVIEW:

A. If the protocol did not qualify for expedited review at the time of initial approval, it typically will not qualify for expedited review at the time of continuing review. However, the IRB chairperson or IRB member designee is authorized to use expedited review procedures for continuing review when either of the following Expedited Review Categories (8 or 9) are met, as described below:

B. **Expedited Review Category (8):** Continuing review of research previously approved by the IRB but where:
   1. The research is permanently closed to the enrollment of new participants; All participants have completed all research-related interventions; **AND**
   2. The research remains active only for long-term follow-up of participants; **OR**
   3. Where no participants have been enrolled at a particular site and no additional risks have been identified by the IRB or PI from any site or relevant source; **OR**
   4. Where the remaining research activities are limited to data analysis.

C. **Expedited Review Category (9):** Continuing review of research not conducted under an investigational new drug application (IND), or investigational device exemption (IDE) where Expedited Review Categories two (2) through eight (8) do not apply, but the IRB has determined and documented at a convened meeting the research involves no greater than minimal risk and no additional risks have been identified.

D. When submitting documents for expedited review, ensure a clean consent and authorization document, assent form (if applicable) and/or an Information Sheet are required.

E. It is the goal of the IRB to mail notice of the results of the expedited continuing review to the PI within one (1) week following the reviewer's decision.

X. FULL BOARD CONTINUING REVIEW:

A. All protocols ineligible for expedited continuing review will be submitted to the full board IRB. The full board continuing review process is as follows:
   1. A primary reviewer will be provided with copies of the continuing review documents, and will have access to the complete protocol file at the time of the review.
   2. Each member of the IRB will be provided with electronic copies of the Progress Report, consent and authorization document, assent form (if applicable), information sheets and any approved advertisements for each of the continuing reviews in advance of the meeting. These materials are submitted as a part of the packet IRB members receive in sufficient time to prepare for each meeting.
   3. At the time of the IRB meeting, the primary reviewer will present his/her findings for each Progress Report and the IRB Chair will open the floor to discussion. In addition to the specific findings of the reviewer, the currently approved consent and authorization document and assent form (if applicable), information sheets and advertisements will be reviewed to ensure:
      a. The currently approved consent and authorization form is accurate and complete AND

b. Any significant new findings possibly related to the participant's willingness to continue participation are provided to the participant, in accordance with HHS regulations.

B. The IRB may receive a summary from a Data Safety Monitoring Board (DSMB) or sponsor indicating a review of study-wide adverse events and unanticipated problems, interim findings, and any recent literature that may be relevant to the protocol has taken place.

C. The IRB review will include reports of local adverse events and other unanticipated problems involving risk to research participants or others, and other relevant information from non-Beaumont research sites needed to ensure its' continuing review is substantive and meaningful.

D. After careful consideration of all materials presented, the IRB members take a vote which is recorded in the following format: number for, number against, number abstained. The outcome of a continuing review may be Approved, Modifications Required, Deferred or Terminated.

E. The minutes of the IRB meeting will reflect deliberations, actions and votes for each continuing review. In addition, protocol identifiers will be included in the minutes: IRB number, study title, PI name and actions taken by the IRB. Copies of the minutes will be distributed to all IRB members for their review and approval prior to the next scheduled meeting.

F. IRB continuing review of greater than minimal risk studies utilizes a Continuing Review checklist when Beaumont IRB serves as the IRB of record. The checklist requires the reviewer to notify the IRB manager when a lapse in approval occurs so the lapse may be immediately addressed. If an external IRB is serving as the IRB of record, then continuation of the research is reviewed by the external IRB and accepted by the Beaumont IRB.

G. The Continuing Review checklist will address cause(s) of any lapse in IRB approval and identify steps taken to prevent future lapses. If the IRB re-approves a study following a lapse in IRB approval, the approval may be granted for one year and a new expiration date established for subsequent review and approval periods. The IRB may choose to re-approve the research for a period of less than one year, either to retain the original anniversary date on which prior approval periods expired or to address study risks.

H. When continuing review of a research project does not occur prior to the end of the IRB specified approval period, IRB approval automatically expires. OHRP and FDA do not consider such an expiration of IRB approval to be a suspension or termination of IRB approval. Therefore, such expirations of IRB approval do not need to be reported as

suspensions or terminations of IRB approval to OHRP under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) or to FDA under 21 CFR 56.113. Repeated lapses and/or continuation of research activities during a lapse without an approved exception may represent serious and/or continuing non-compliance and be subject to the IRB reporting requirements.

XI. SUSPENSION OR TERMINATION:

A. If the IRB notes a pattern of non-compliance with the requirements for continuing review (e.g., a PI repeatedly or deliberately neglects to submit materials for continuing review in a timely manner, or the IRB is not meeting the continuing review dates), the IRB should determine the reasons for the non-compliance and take appropriate corrective actions. The IRB must report to the FDA any instance of serious or continuing non-compliance with the FDA regulations, IRB requirements or determinations, and any suspension or termination of IRB approval. The IRB will notify the sponsor of any instance of serious or continuing non-compliance with the FDA regulations, IRB requirements or determinations, and any suspension or termination of IRB approval. See policy *Contacts, Complaints, Allegations of Non-Compliance and Confirmed Non-Compliance in Clinical Research*.

B. Any suspension or termination of IRB approval must include the reasons for the IRB's actions and be promptly reported to the PI, institutional officials, and the FDA. The report will include:
   1. The name of the drug, device or biologic;
   2. The IND number or the IDE number/non-significant risk (NSR) status of the device;
   3. The full name of the research protocol;
   4. The name(s) and addresses of the clinical investigator(s);
   5. The reason for the suspension or termination; and
   6. Information about the IRB's investigation and action plan to prevent/address future non-compliance.

C. When a study is suspended or terminated by the IRB, the IRB should consider the need to inform current or previously enrolled study participants, as appropriate, about the action. In addition, the IRB should ensure the rights and welfare of currently enrolled participants are protected. Participants should not be put at risk and should receive appropriate care if indicated, should the IRB (a) suspend or terminate during the period for which IRB approval had already been given; or (b) disapprove the study at time of continuing review.

D. IRB consideration of what is in the best interest of the enrolled participants should include:
   1. Continue receiving the interventions being administered to participants under the study at the present site.
   2. Be transferred to another study-site so participation in the study may continue, or
   3. Be transitioned to medical management outside of the research context.

E. Continuation of participants on the test article may be appropriate i.e., when the test article holds out the prospect of direct benefit to study participants or when withholding the test article poses increased risk to study participants. If the IRB decides the enrolled participants should continue to receive the test article, it should also ensure data collection for safety information continues for the participants. If follow-up of currently enrolled participants is necessary to ensure their rights, safety or welfare, the IRB should ensure the PI informs the participants, and reports any unanticipated problems to the IRB, sponsor and the FDA.

XII. POST FULL BOARD MEETING PROCEDURES:

Notification of the results of the full board continuing review will be signed by the IRB Chair and sent to the PI approximately one (1) week following the IRB meeting. Once a PI responds in writing to all IRB concerns, the response is attached to the study file (which includes a copy of the IRB's deliberations) and is provided to the IRB Chair, IRB member designee, or full committee for their review and approval. If the continuing review was deferred, it will be returned to the full committee. The reviewer's comments will be documented and another letter will be sent to the PI. If all requirements are met, the continuing review approval letter will be sent to the PI. The approval will be entered into the IRB database, and appended to the protocol in chronological order.

XIII. FINAL STUDY CLOSURES:

A. If the study is to be closed, the PI must complete the Final Report / Closure Form. The form requires information about the progress of the study, which includes:
   1. Effective date of closure;
   2. Reason for closure;
   3. Date project closed to participant enrollment;
   4. Date participant follow-up completed;
   5. The number of study participants, both local and overall.

B. Verification of IRB receipt and notice of study closure will be returned to the PI.

XIV. APPLICABLE REGULATIONS AND GUIDELINES:

45 CFR 46.103(b)(4) Assuring Compliance,
45 CFR 46.108(b) IRB Functions and Operations
45 CFR 46.103(a) Unanticipated Problems Involving Risks and Adverse Events guidance
45 CFR 46.103(b)(5) Guidance on reviewing and reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events
45 CFR 46.109(e) IRB Review of Research
45 CFR.111) Criteria for IRB Approval of Research
45 CFR 46.116(b)(5).
21 CFR 56.103(a) Circumstances in which IRB Review is required
21 CFR 50.25(b)(5).
21 CFR 56.113 Suspension or termination of IRB approval of research
21 CFR 312.50 Ensuring compliance with plan and protocol
21 CFR 312.53 Selecting investigators and monitors
21 CFR 312.60 General responsibilities of investigators
21 CFR 812.40 General responsibilities of sponsors
21 CFR 812.43 Investigational Device Investigations Selecting investigators and monitors

Guidance for IRBs, Clinical Investigators, and Sponsors-IRB Continuing Review after Clinical Investigation Approval February 2012 OHRP Guidance, "Categories of Research that may be Reviewed by the Institutional Review Board (IRB) through an Expedited Review"

XV. REFERENCES TO OTHER APPLICABLE POLICIES:

IRB policy *Expedited Review of Research*
Research policy *Contacts, Complaints, Allegations of Non-Compliance and Confirmed Non-Compliance in Clinical Research*
IRB policy *Review by an External Institutional Review Board*
IRB policy Criteria for Determining Frequency of Review by the IRB

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.