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DATA AND SAFETY MONITORING		**207**	
Prepared By	Prior Issue Date	Issue Date	
Institutional Review Board	**7/7/15**	**2/22/2018**	

PURPOSE

The purpose of this policy is to provide guidelines for data and safety monitoring plans for human participant research being conducted at Beaumont Health (Beaumont).

SCOPE

This policy applies to Beaumont investigators, key personnel, Scientific Review Committee (SRC) members, Institutional Review Board (IRB) members, IRB staff and individuals who accept responsibility for monitoring data and safety in Beaumont research.

BACKGROUND

In accordance with federal regulations, institutions engaged in human participant research must have written procedures for ensuring the safety of human participants involved in greater than minimal risk research. According to the National Institute of Health (NIH) and the Food and Drug Administration (FDA) guidelines, all clinical trials require some level of safety monitoring. The type of monitoring is dependent on the inherent level of risk, the size and the complexity in the proposed research. For greater than minimal risk investigator initiated trials, an SRC will evaluate the proposed data and safety monitoring plan. For all studies, the IRB of record is also responsible to review the data and safety monitoring plan to assure it is appropriate to the level of risk for the proposed study. The SRC or IRB may require modifications to the proposed safety plan, if deemed inadequate.

Data and safety monitoring are separate from clinical, regulatory and quality monitoring. The latter assess clinical trial operations and conduct to assure regulatory, policy and protocol compliance, in addition to validating data management practices to assure integrity of data and reporting of results. However those responsible for monitoring data and safety should carefully consider how concerns in these areas (clinical, regulatory and quality) may impact participant safety and outcomes or the integrity of study findings. It would be inappropriate to subject future participants to research associated risks if it is believed the study will not result in a meaningful outcome.

External study sponsors (e.g. commercial, sub-contractors, cooperative group, other NGO's) are responsible to provide Beaumont principal investigators (PI) with a study specific data and safety monitoring plan designed to assure ongoing safety of research participants, as well as copies of data and safety monitoring reports throughout the study. The Beaumont PI will submit a copy of the data and safety monitoring reports to the IRB of record, according to each IRB's policies.

POLICY

It is the policy of the Beaumont Research Institute and IRB to protect the rights of all individuals taking part in human participant research. To ensure participant safety, all Beaumont investigator initiated, greater than minimal risk clinical protocols must include a data and safety monitoring plan at time of submission to an SRC and the IRB.

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DEFINITIONS

Investigator-Initiated Study	Research proposed by an individual Beaumont representative (i.e., employed or affiliated individual) with little or no involvement from an outside sponsor. Research may be conducted solely at Beaumont or may include multiple sites.
Independent Study Monitor(s)	A physician or group of individuals (with a least one physician) charged with evaluating safety data. Independent study monitors (also known as medical monitors) are required to track the safety review of data and provide findings, in writing, to the PI. The individual(s) may not be key personnel on the study. While the data and safety monitoring plan should be specific about timing of the monitoring, regularly scheduled meetings or a charter are not required. The use of independent monitors should be limited to: 1) early phase or pilot studies of greater than minimal risk; 2) low/minimal risk studies (as determined by the SRC or IRB), including Phase 4 studies of approved drugs/devices; or 3) to supplement additional types of safety monitoring.
Data and Safety Monitoring Plan	A data and safety monitoring plan (DSMP) is a study specific plan developed by the study sponsor or sponsor investigator, outlining how study progress will be monitored throughout the course of the research to ensure the safety of participants and the integrity and confidentiality of data.
Data Safety Monitoring Committee (DSMC)	An independent group of experts who advise the sponsor or sponsor-investigator concerning data and safety of the study. The primary responsibilities of the DSMC are to: 1) periodically review and evaluate accumulated study data for participant safety, study conduct and progress, and when appropriate, efficacy; and 2) make recommendations to the sponsor or sponsor investigator concerning the continuation, modification, or termination of the study.
Non-affiliated Individual	An individual who has no discernible ties, ongoing relationship, or association with Beaumont or the PI.
Independent Individual	A person uninvolved in the development or conduct of the proposed research, with no reporting relationship to the PI, no business or partner relationship to investigators in the study or other relationships who could influence their objectivity during the review. An independent individual may be affiliated or non-affiliated with Beaumont, and may be from the department conducting the research. Examples include physicians with similar clinical expertise within the department, research nurses not involved in the study and/or a biostatistician not involved in the design or analysis of the study.
Pilot Study	A small scale-study conducted prior to conducting an actual experiment; designed to test and refine procedures.
Sponsor/Investigator	An individual who both initiates and conducts an investigation. A sponsor-investigator is responsible to fulfill all of the responsibilities of a

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sponsor and of the PI, including, but not limited to, data and safety monitoring, investigational drugs or devices used in the study and filings with the FDA.

EXAMPLES OF RECOMMENDED MONITORING BY STUDY TYPE

Type of Study	Examples	Recommended level of data and safety monitoring *
Level I Studies Observational studies or interventional studies using procedures generally considered as minimal/low risk	- Post market studies - Infrequent peripheral blood draws - Nasal wash - Nutritional assessments - Questionnaires - Behavioral surveys - Imaging without sedation, IV contrast or significant additional radiation (i.e. non standard of care CT scan - Use of left over samples from clinically indicated procedures - EKGs - Gait assessments	PI only or study team
Level II Studies Interventional studies using procedures or treatments with well-established risk profiles	- Imaging requiring sedation, IV contrast or significantly more radiation than would be clinically indicated - Nutritional therapies - Low risk procedures (e.g., endoscopy, glucose-tolerance tests, induced sputum, skin biopsy, lumbar puncture, bone marrow biopsy, imaging requiring sedation) - Therapeutic trials involving licensed agents with known safety profiles and without reason to suspect the safety profile would be different for the proposed indication or age group	PI only or study team. May benefit from having an independent data and safety monitor.
Level III Studies (a) Minimal or low risk interventional studies targeting children or psychologically or cognitively impaired individuals		Independent data and safety monitor or data and safety monitoring committee
Level III Studies (b) Interventional studies using procedures or treatments generally considered to be moderate-risk	- Insulin clamp studies - Organ or muscle biopsy - Phase II single site or multi-site trials of agents with available safety data in the same population - Therapeutic trials involving licensed agents with known safety profiles and with unknown impact on safety to the targeted population	Independent data and safety monitor or data and safety monitoring committee
Level IV Studies Interventional studies involving investigational agents or devices that present substantial risk to study participants	- Investigator initiated IND of IDE studies - Phase I multi-site trials - Gene therapy - Phase III randomized blinded comparative trials - High-risk clinical procedures if performed solely for research purposes	Data and safety monitoring committee generally required

RESPONSIBILITIES

Sponsor/Investigator

The sponsor-investigator must ensure appropriate data integrity and participant safety monitoring occurs throughout the conduct of the study. Details of the monitoring plan must be included in the study protocol (or protocol attachment) and provided to the SRC (when investigator

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initiated) and the IRB of record during the initial review of the proposed research. Data entry, clinical, regulatory and quality monitoring must be conducted timely to assure data reviewed by the independent monitor(s) and/or DSMC is complete and properly reflects the clinical trial activities. The sponsor-investigator must assure data and safety monitors are engaged and operating in accordance with the data and safety monitoring plan. In the event individual(s) engaged to conduct the monitoring are not complying with the plan (i.e., scope, frequency, reporting), the IRB of record should be notified and the individual(s) replaced. Results of ongoing safety monitoring by the independent monitor(s) and/or DSMC must be submitted to the IRB on a regular basis, consistent with the plan outlined in the IRB approved protocol.

For observational, minimal or low risk studies, the sponsor-investigator may accept direct responsibility for monitoring the data and safety of research participants. This must be specifically stated in the data and safety monitoring plan and approved by the SRC (if SRC review is required) and/or the IRB of record.

Scientific Review Committee

All greater than minimal risk, investigator initiated clinical trials conducted at Beaumont must undergo formal scientific review prior to submission to the IRB. Select minimal risk investigator initiated clinical trials may be required to undergo SRC review. The purpose of scientific review is to assure the study design meets the intended scientific goals, while limiting participant risk. Scientific review related to the data and safety monitoring plan includes, but is not limited to:

- Does the protocol schedule/table of events include all protocol required activities?
- Does the protocol clearly/accurately identify and describe risks to participants or others?
- Does the study use appropriate methods or procedures to minimize risk?
- Is the protocol's assessment of risks, benefits and measures used to minimize risk scientifically accurate?
- Is review of concomitant medications addressed (i.e., method of collection, any which do not require capture)?
- Are the definitions of adverse events clear and comprehensive? Is the quantification of adverse events described?
- Is the plan for reporting Unanticipated Problems (UPs), Adverse Events (AEs), and Serious Adverse Events (SAEs) clear and appropriate?
- Based on the study risks, is the type of monitoring appropriate (e.g., medical monitor, data safety monitoring committee, formal Data Safety Monitoring Board)?
- Is the composition/expertise of the Independent Monitor or DSMC appropriate?
- If DSMC is required: are the review plan and triggers requiring DSMC action clearly stated?

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Institutional Review Board	Review of data and safety monitoring plans are a regulatory requirement for all IRB's. When the Beaumont IRB is the IRB of record, their review will include appropriateness of the proposed data and safety monitoring plan, evaluation of review time points, and composition of any proposed committees (if applicable).
Independent Monitor(s)	Responsibilities of the independent monitor(s) must be delineated in the data safety and monitoring plan, including information to be reviewed (e.g., post procedure assessments, 30 day outcomes, serious adverse events) and review time points (e.g., after each patient, after the first 5 patients, quarterly). The independent monitor's duties should be based on specific risks or concerns about the research. The independent monitor may be identified from within Beaumont or from an external organization. The independent monitor(s) must provide a written summary of each review completed. An independent monitor may be used to supplement a DSMC e.g., for studies involving life-threatening diseases, diseases with serious morbidity, vulnerable populations who could not decide to leave trial, or novel treatments with potential for serious adverse events. A biographical sketch or CV and evidence of human subject protection training for the independent monitor must be maintained in the research records. There should be no apparent conflict of interest and the monitor cannot be under the supervision of the PI or other investigators or research staff. If the duties of the independent monitor could require disclosure of subjects' Protected Health Information outside a covered entity (i.e., the research monitor is not an agent of the covered entity), the PI's institution may require the identity and location of the independent monitor to be described in the study informed consent and authorization document provided to participants.
Data Safety Monitoring Committee	Responsibilities of the DSMC will be detailed in either the protocol or a separate Data and Safety Monitoring plan, including committee composition, frequency and setting for meetings (phone conference or web based meetings are acceptable; communicating by email is not an acceptable method for meeting) and the scope of their review. All members of the DSMC should become familiar with protocol requirements. It is suggested the DSMC prepare a checklist of review materials to assure a complete review is conducted at each meeting. At the conclusion of their review, the DSMC must determine if recommendations concerning continuation of the study or changes to the protocol or operations should be considered or required. The PI must submit DSMC's reports and/or formal checklists used to document their review, to the IRB of record according to their policies.
Independent Monitor for DoD Research	For research determined to be greater than minimal risk, DoDI 3216.02 requires the IRB approve, by name, an independent research monitor with expertise congruous with the nature of risk(s) identified within the research protocol. The IRB or organizational official may require an

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independent monitor for a portion of the research or studies involving no more than minimal risk, if appropriate. The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities.

Independent monitor functions for DoD studies may include:

- observing recruitment and enrollment procedures and the consent process for individuals, groups or units,
- overseeing study interventions and interactions,
- reviewing monitoring plans and reports,
- overseeing data matching, data collection, and analysis.

There may be more than one independent monitor (e.g., if different skills or experiences are necessary). The monitor may be an ombudsman or a member of the data safety monitoring board. At a minimum, the independent monitor:

- may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research;
- have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report;
- have the responsibility to promptly report their observations and findings to the IRB or other designated official and the funding agency.

REGULATORY REFERENCES

21 CFR 56.111(a)(6) - Criteria for IRB Approval
45 CFR 46.111(a)(6) - Criteria for IRB Approval

OTHER REFERENCES

Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

Information for Investigators: Headquarters, U. S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP)

Human Research Protections Regulatory Requirements
Data Monitoring Committees, Establishment and Operation of Clinical Trial, Guidance for Clinical Trial Sponsors
http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm

ASSOCIATED POLICIES

Research policy *Scientific Review Committee Process*
IRB and Clinical Research Policy *IRB Initial Review of Research Protocols*
IRB and Clinical Research Policy *Expedited Review of Research*

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