WMREF Institutional Review Board
Policies & Procedures

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I. IRB MISSION

A. Purpose

1. The mission of the Wichita Medical Research and Education Foundation's Institutional Review Board is to safeguard the rights and welfare of human research subjects – both before and throughout their involvement in a medical research study. This impartial review panel performs the job of risk/benefit assessment ensuring that the risks are both minimized and fairly disclosed to study participants in any medical human research including the testing of drugs, vaccines, medical devices, and new medical procedures.

B. Policy

1. Wichita Medical Research and Education Foundation's Institutional Review Board has the authority to approve, require modifications, or disapprove the proposed study protocols and consent forms that will involve human subjects. In addition, the IRB reviews and approves or disapproves the investigator for the research, based on the curriculum vitae of the investigator, and, when applicable, recommendation of the appropriate Medical Staff department. Once approved, the IRB monitors the progress of ongoing research.
2. WMREF IRB is not affiliated with any contract research organization (CRO) or pharmaceutical or device sponsor.

II. IRB AUTHORITY AND INSTITUTIONAL RESPONSIBILITIES WITH REGARD TO HUMAN SUBJECT PROTECTION

The WMREF Institutional Review Board (IRB) has been established by Wichita Medical Research and Education Foundation in accordance with federal law to ensure that human subjects participating in research activities sponsored by or involving a contracting hospital, clinic, or physician's office are protected from undue risks or deprivation of personal rights and dignity. The IRB has the ultimate responsibility to review human subject research and the authority to approve, require modification in, or disapprove such research, unless the IRB Chair and/or his designee have specifically exempted the activity from IRB review.

The IRB also has the authority to require progress reports from the investigators, to oversee the conduct of the studies, to suspend or terminate approval of a study, and to place restrictions on a study. (FDA Information Sheets, Appendix H, IV, C-E)

The WMREF Institutional Review Board acts under contract with Wesley Medical Center to provide IRB services and oversight for all human research to be carried out at Wesley Medical Center and/or one of its affiliates. It may, in addition, provide review and oversight of research not affiliated with Wesley Medical Center.

The IRB works under the auspices of federal, state, and local law. The FDA and OHRP (Office for Human Research Protection) are the two federal agencies with which the IRB most frequently cooperates. These two agencies are available for guidance on issues that arise, and are overseers of the work of the IRB.

Note: All references to 21 CFR §56 and 21 CFR §50 throughout this document can also be found in 45 CFR §46, usually at the identical citation (such as 21 CFR §56.107(f) and 45 CFR §46.107(f)), unless otherwise noted.

III. IRB MEMBERSHIP

A. Committee Composition

1. The IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If the IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects. (21 CFR §56.107(a))

2. Every nondiscriminatory effort will be made to ensure that the IRB does not consist entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. The IRB may not consist entirely of members of one profession. (21 CFR §56.107(b))

3. The IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.
(21 CFR §56.107(c))

4. The IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. (21 CFR §56.107(d))

5. The IRB may not have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. (21 CFR §56.107(e))

6. The IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB. (21 CFR §56.107(f))

7. IRB members are appointed to a one-year renewable term by the President of the Wichita Medical Research and Education Foundation Board of Directors. New members will attend two IRB meetings as non-voting members and go through an orientation with the IRB Director or someone else on the IRB Staff before attaining voting status. (FDA Information Sheets [FIS] Appendix H, VII ,B, C)

8. The IRB Chair is elected by the Board of Directors of the Wichita Medical Research and Education Foundation.
   a. The Chair of the IRB shall be selected considering the following qualifications:
      i. The individual should have experience on the IRB and be a member in good standing.
      ii. The individual should have a good understanding of the Code of Federal regulations as they apply to the protection of human subjects in research and the policies of the IRB.
      iii. The individual should have enough time at his/her disposal to perform the duties and responsibilities of the Chair.
      iv. The term of the Chair is open ended.
      (FIS Appendix H, VII, A.)

   b. The duties of the Chair include the following:
      i. Chair the scheduled IRB meetings.
      ii. Communicate with the IRB Office on a regular basis.
      iii. Discuss IRB concerns with research investigators.
      iv. Provide emergency and/or administrative approval.
      (FIS Appendix H, VII, A)

9. The Chair votes as an active member of the Board. (FIS Appendix H)

10. In the event of a tie vote, discussion will continue and a second and, if necessary, third vote will take place. If there is still a tie after three votes, the item will be tabled to the next IRB meeting.

11. The IRB Vice-Chair(s) is/are appointed by the President of the Wichita Medical Research and Education Foundation (WMREF) Board of Directors (BOD). The Vice-Chair(s) vote(s) as active member(s) of the Board. The Vice-Chair(s) will step in for the Chair in his/her absence or during the Chair's recusal. If the Chair and Vice-chair(s) are not able to chair a meeting the IRB Director may chair the meeting as a voting member with the stipulation that all other required representation is convened.
    (FIS Appendix H)

12. Alternate members help to provide a quorum and keep the board diversified when a member is unable to attend an IRB meeting. Each alternate member must have qualifications similar to the member he/she replaces. The member(s) an alternate may replace must be designated at the time of the appointment of the alternate, and is listed as such in the IRB Roster of Members. Alternate members are appointed by the President of the WMREF BOD for a one-year renewable term. Alternate members will be notified and provided with all of the materials in advance of a meeting they will attend for a regular member. They will have full voting status at that time. (FIS Appendix H and page 7)

13. A roster of members and alternates is updated annually with a new date, even if there have been no membership changes. The IRB is registered with the OHRP. This registration is mandatory.

14. IRB Members are not monetarily compensated by WMREF for their time and efforts. A meal is provided for each meeting. (FIS Appendix H, VII, D.)

15. Liability coverage for IRB members and alternates is provided by Wichita Medical Research and Education Foundation. (FIS Appendix H, VII, E.)

16. No voting by proxy is permitted. (FIS Appendix H, IX, E)

17. The IRB follows the Code of Federal Regulations regarding the inclusion of human subjects in research, following both the FDA and the HHS (NIH) regulations. The WMREF Institutional Review Board is also guided by the Ethical Principles set forth in the Belmont Report. This Policy is not meant to duplicate the Code of Federal Regulations and lack of specific citations should not be interpreted as lack of compliance by this IRB.

B. Qualification of New IRB Member

The following procedures will be used in evaluating and selecting members for the Institutional Review Board.

1. When the IRB, IRB Office, and/or Board of Directors determines that a new member is necessary for the functioning of the IRB, the current membership and Office shall suggest possible candidates for consideration by the President of the WMREF Board of Directors. The IRB may request these candidates provide the IRB Office and Board President with a copy of their resume for the Office and President of the WMREF Board of Directors to review.
2. The IRB Chair and Director will review candidates for the following qualifications:
    a. The candidate has expertise which is necessary to the functioning of the IRB and which is either not currently present on the Board or needed in addition to the current IRB membership.
    b. The candidate will be able to review meeting materials prior to each meeting, provide the Chair with comments prior to the meeting if requested to do so, and be able to attend most or all of the IRB meetings during the course of the year.
3. Candidates are recommended to the President of the Board of Directors of WMREF, who has authority to appoint members to the IRB. (FIS Appendix H, VII, B)
4. Each IRB member and alternate will sign a Confidentiality Statement and Conflict of Interest Form when they initially become a part of the Board and annually thereafter.

C. IRB Member Attendance

IRB members are expected to attend the majority of meetings and notify the IRB Director or IRB Office of any absence. If an IRB member fails to attend a minimum of 50% of IRB meetings, that member can be removed from active IRB membership. (FIS Appendix H, VII, B)

D. Quorum

A majority of the IRB membership constitutes a quorum. "Quorum" is defined as a majority of all IRB members. Thus if there is an even number of IRB members on the roster, one more than half of all members

constitutes a quorum. If there is an odd number of IRB members on the roster, that number one-half greater than 50% constitutes a quorum. A quorum is required in order to approve, modify, table, or disapprove a protocol or any other item of business. With a quorum present, a decision is made with the vote of the majority of those members present.

An IRB member whose responsibilities are primarily in nonscientific areas must be present at a convened meeting before the IRB can conduct its review of research. The IRB will not have a member participating in initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the Board. A member who is licensed to prescribe drugs must be present when an investigational drug study is reviewed.

A member may attend the meeting through teleconference or speaker phone, but may only count as part of the quorum and vote for items for which he/she has the same materials as the members physically in attendance.

E. Removal of IRB Member

The following procedures will be used in removing a member from the IRB.

1. To remove a member from the IRB, there must be just cause shown of that member's inability or unfitness to serve on the Board. Just cause for removal may be lack of minimum attendance, lack of participation at meetings as judged by the IRB Chair, misconduct, or unresolved conflict of interest.
2. The removal of a member from the Board requires approval of the President of the WMREF Board of Directors. (FIS Appendix H, B)

F. Removal of the IRB Chair

The IRB Chair can be removed for cause only by the President of the Wichita Medical Research and Education Foundation Board of Directors or by a vote to remove by three- fourths (75%) of the WMREF Board of Directors. (FIS Appendix H, A)

IV. IRB FUNCTIONS AND OPERATIONS

A. Meeting Scheduling

The IRB meets as often as is necessary to conduct its business. The general schedule is to meet on the third Wednesday of each month. The meeting schedule is mailed to all IRB members at the beginning of each year. Conflicts with holidays may result in moving the date of a meeting. The IRB does not meet at a scheduled time if there is not sufficient business to hold a meeting.

The exact time and location of each meeting will be delivered to each member with each month's meeting agenda and material for review.

B. "Integrated" Feedback to Investigators

1. **Comment Sheets and Revision Recommendations**

As frequently as possible, IRB members shall write down (in paragraph form) the substance of comments and questions from the time of their receipt of the packet through the end of the meeting on the comment sheets provided with members' packets. These comments should be prioritized by each member before turning them in. The comment sheets will be signed and handed to the WMREF staff at the conclusion of each IRB meeting, so that they may be incorporated into the minutes and into correspondence with investigators whose research is under review.

For new studies, the Primary Reviewer will also review both the IRB Consent Checklist and HIPAA Authorization Checklist (unless not applicable to the study), marking any deficiencies to be discussed at the meeting. These are to be turned in to the IRB staff at the end of the meeting. Name of protocol and signature and date of reviewer are required. These will be placed in the study file in the IRB Office.

During the meeting, the Chair of the IRB and/or Director will serve as a filter and organizer for IRB comments and questions back to the investigator. Irrelevant comments or questions need not be directed to the investigator. At the conclusion of each discussion, the Chair and/or Director will ask for the IRB members' help in prioritizing comments and questions, so that major issues (vis-à-vis human subject protections) are clearly distinguished from minor issues. If some of the comments or requests are inconsistent or contradict one another, the IRB Chair will ask for the IRB members' help in rendering a clear, consistent communication to the investigator.

2. **Determining Length of Approval**

The length of time until the next scheduled review of the protocol shall be based on IRB judgment about the degree of risk posed by the study. Ordinarily, the WMREF IRB will schedule continuing reviews at intervals of twelve months. However, each study will be evaluated for approval length according to the following criteria:

a. The level of risk the study poses;
b. The status of the study investigator; this includes:
    1. General clinical research experience,
    2. Experience with the specific procedure, drug, or device,
    3. Past performance in IRB approved research, and
    4. Adherence to IRB regulations.

c. The adequacy of the investigator support staff
d. Any confounding issues pertaining to the research study being reviewed.

The IRB membership will determine an appropriate review schedule, which may be based on less than a 12 month review, the number of patients enrolled, a combination of the two, or any other restrictions the IRB deems appropriate. Approval maximum is one year (12 months), at which time a continuing review and approval is required for the study to remain active.
(21 CFR §56.108(a)(2) and §56.109(f))[1]

3. Formal Notification of the Principal Investigator

A formal letter will be sent from the IRB Office to each principal investigator following the IRB Meeting. The letter will explain whether the proposed research was approved, needs modifications before approval, or was disapproved. In the latter two instances, the reasons for the IRB decision will be delineated. If the study has connections with Wesley Medical Center, a copy of the letter of approval (only) will be sent to the "point of contact" at the institution, per the agreement between WMREF and WMC. (21 CFR §56.108(a)(1), §56.109(e)) Copies of letters requiring modifications will not be sent to Wesley.

If the letter contains modifications needed before approval, it will also include a statement regarding the deadline to submit modifications to the IRB Office. The letter will state, "Modifications are required to be submitted to the WMREF IRB Office no later than 90 days from the date of the letter of notification to the investigator. If modifications are not received by this date, your study proposal will be administratively terminated." In addition, two weeks before the date of termination, the IRB Office will notify the Principal Investigator by mail or electronic mail that the study is due to expire on the specific date.

If the proposal is approved, the letter to the principal investigator will include the following:

a. Any deviation from the protocol or the informed consent document will require prior approval from Wichita Medical Research and Education Foundation's IRB, except when necessary to eliminate apparent hazards to human subjects, in which case notification to the IRB is required.
b. The study may not commence until staff education has been accomplished with all affected departments impacted by the study.
c. It is the investigator's responsibility to coordinate the research study with the affected departments prior to the start of the study. This may also require determination of cost reimbursement to the departments involved.
d. The principal investigator (research physician) is responsible for:
    1. Coordinating all research aspects of medical care provided to patients who are research subjects.
    2. Providing information about the research risks and benefits to the patient.
    3. Obtaining written informed consent and HIPAA authorization from each patient enrolled in the research study, unless these have been waived by the IRB.
    4. In cases where the principal investigator is not the attending physician, the principal investigator is also responsible for coordinating the

research activity with the attending physician and consulting physicians and for providing them with information regarding the nature of the research.

[1]Also 45 CFR §46.103(b)(4) and 45 CFR §46.109(e)

5. Reporting immediately any complications, adverse effects or other changes in research activity that arise to the Chair of the Institutional Review Board. (21 CFR §56.108(a)(3))[2]

6. Furnishing the IRB Office with reports of the research every twelve months (or other shorter period of time as designated by the IRB) and when the research is completed, giving the number of patients involved and the results of the research.

7. Complying with continuing review requirement in conjunction with OHRP and/or the FDA.

(21 CFR §56.108(a)(1) and §56.109(e))

A copy of the template for this letter is provided in the Appendix.

IRB approval letters may be signed by the IRB Chair or Vice-Chair(s). The IRB Chair may, with a letter of designation, authorize the IRB Director and/or the Research Administrative Secretary to sign letters and other correspondence for him/her. (FIS page 10, Q.29)

The IRB does not have a formal appeal process for a proposal that is disapproved. However, if revisions are made as outlined in the letter to the Principal Investigator, the proposal may be resubmitted for consideration at the next IRB meeting after resubmittal to the IRB Office. The proposal can also be brought back without changes for reconsideration. The Principal Investigator should submit reasons and references as to why the IRB should reconsider a decision concerning a revision. A third review will not be considered without any changes having been made in the proposal.

C. Minutes of IRB Meetings

1. **Contents**
   The minutes will be compiled by the Research Administrative Secretary or another IRB staff member, with the assistance of the IRB Director. Minutes of IRB meetings shall be in sufficient detail to show attendance at the meetings, actions taken by the IRB, the vote on these actions including the number of members voting for, against, and abstaining, the basis for requiring changes in or disapproving research, and a written summary of the discussion of controverted issues and their resolution. A listing of any guests/consultants present during the meeting will be so recorded separately from the member listing. (21 CFR §56.115(a)(2))

2. **Review and approval**
   The initial draft of the minutes of IRB meetings will be presented by inter-institutional mail, facsimile, U.S. Mail, and/or as an e-mail attachment to all members. Members are asked to contact the WMREF IRB Office with their comments on the minutes in one of three ways. If the members find the minutes satisfactory as presented, they may call in approval. If there are changes found,

these are to be clearly noted and sent either via e-mail or signed and dated facsimile. A second draft with all corrections incorporated will be presented for final vote at the next IRB meeting. Members may again request amendments to the minutes, should errors be found. Once the minutes have received final approval, any tapes and/or previous drafts will be destroyed. Access of the minutes is restricted to IRB members and staff, agencies and departments of Federal oversight, the Wichita Medical Research and Education Foundation Board of Directors, and as required by law.

[2]Also 45 CFR §46.103(b)(5)

D. Conflict of Interest

For purposes of IRB deliberations, "conflict of interest" pertains when an IRB member (a) is directly (as a co-investigator) involved with a protocol under consideration, (b) has any financial stake (direct or indirect) in the protocol, or (c) feels he/she cannot be totally objective about the review due to collegial or social ties with one or more of the investigators. The possibility of "conflict of interest" pertains when an IRB member is indirectly (as a peripheral collaborator or Director) involved with the protocol. An IRB member should always declare a "conflict of interest" promptly whenever the protocol in question comes up for consideration. In situations where the IRB member detects the possibility of a "conflict of interest," the IRB member should declare this possibility to the IRB Chairperson and (in a discussion with the IRB) make a decision about whether or not to excuse him/herself. (21 CFR §56.107(e))
Each IRB member and alternate will sign a Conflict of Interest Statement when they initially become a part of the Board and annually thereafter.

Polling for conflict of interest will occur at each IRB meeting before any items requiring a vote are discussed or otherwise considered.

E. Criteria for IRB Approval of Research

In order to approve a specific submitted research proposal, the IRB must determine that all of the following requirements are satisfied:

1. Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.(21CFR§56.111(a)(1))

2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility. (21 CFR§56.111(a)(2))

3. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will

be conducted, and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.(21CFR§56.111(a)(3))

4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative.(21CFR§56.111(a)(4))

5. Informed consent will be appropriately documented.(21CFR§56.111(a)(5))

6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.(21 CFR§56.111(a)(6))

7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. (21 CFR §56.111(a)(7))

8. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects. (21 CFR §56.111(b))

See also Further Criteria for Approval of Research with pregnant women, human fetuses and neonate in IV. F, and Requirements for Permission by Parents or Guardians and for Assent by Children in V. D.

F. Further Criteria for Approval of Research with Pregnant Women, Human Fetuses and Neonates

The IRB shall approve research involving pregnant women or fetuses only if all of the following conditions are met:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses; (45 CFR §46.204(a))

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means; (45 CFR §46.204(b))

3. Any risk is the least possible for achieving the objectives of the research; 45 CFR §46.204(c))

4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the

informed consent provisions as recorded in Section V, A-H (45 CFR 46, Subpart A); (45 CFR §46.204(d))

5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions as recorded in Section V, A-H (45 CFR 46, Subpart A), except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy results from rape or incest. (46 CFR §45.204(e))

6. Each individual providing consent under 4 or 5 above in this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate; (45 CFR §46.204(f))

7. For children as defined in 45 CFR §46.402(a) who are pregnant, assent and permission are obtained in accord with subpart D of 45 CFR §46; (45 CFR §46.204(g))

8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy; (45 CFR §46.204(h))

9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; (45 CFR §46.204(i) and

10. Individuals engaged in the research will have no part in determining the viability of a neonate. (45 CFR §46.204(j))

(Also see the IRB Checklist for Research in Pregnant Women or Fetuses on website.)

G. Possible IRB actions

During the review of a research proposal, the IRB may determine that there is not sufficient information or time to make a decision about the protocol. In this case, the IRB may decide to "table" the protocol until a subsequent meeting. If more information is required, the IRB will list the information required and the reasons why the information is necessary, and then pass this list on to the IRB staff as the basis for a letter to the principal investigator.

When the IRB does take action on a newly-submitted protocol, four types of action are possible. When a quorum is present, a protocol may be voted to be "approved," "disapproved," "tabled pending modifications," or "approved pending verification of revisions" by the majority of those members present. The "tabled" category is used when proposals requiring major (substantive) modifications must come back to the full board for review. The "approved pending verification of revisions" category may be invoked when the IRB determines that:

1. the only changes required for approval are minor ones;
2. the required changes have been detailed in writing by the IRB; and
3. the IRB has specified the person responsible (e.g., one or more IRB members; the IRB Director) for verifying that the required changes were made. If not specified, this will be the IRB Director.

Whenever the convened WMREF IRB approves a research proposal, the IRB will simultaneously make two related determinations:

1. whether or not the proposal is judged to represent "minimal risk" research activity*; and
2. the time to next review (never more than 365 days).

*When children are potential subjects, the additional pediatric risk categories will be included in the risk assessment.

If an investigational device is involved, the IRB will also decide whether the device poses a Non-Significant Risk or a Significant Risk.

The length of time until the next scheduled review of the protocol shall be based on IRB judgment about the degree of risk posed by the study. Ordinarily, the WMREF IRB will schedule continuing reviews at intervals of twelve months. However, each study will be evaluated for approval length according to the following criteria:

1. The level of risk the study poses;
2. The status of the study investigator; this includes:
    a. General clinical research experience,
    b. Experience with the specific procedure, drug, or device,
    c. Past performance in IRB approved research, and
    d. Adherence to IRB regulations.
3. The adequacy of the investigator support staff
4. Any confounding issues pertaining to the research study being reviewed.

The IRB membership will determine an appropriate review schedule, which may be based on less than 12-month review, the number of patients enrolled, a combination of the two, or any other restrictions the IRB deems appropriate. (21 CFR §56.108(a)(2) and §56.109(f))

The IRB may request an update or periodic review from any investigator at any time. The IRB may, from time to time, conduct such additional reviews as may be necessary to assure that compliance with policies, regulations, guidelines, and pertinent law is satisfactory. (See also “IRB Monitoring of Ongoing Research”.)

By identifying "minimal risk" studies at the time of initial approval, the IRB may identify a subset of studies that are likely to qualify for continuing review via the Expedited Review procedures.

Investigators will be informed as to the actions of the IRB pertaining to their research by a letter. This letter will detail approval, disapproval, or proviso approval with the details for the decision for each of the last two categories of decisions. If the study involves Wesley Medical Center or one of its entities or its personnel, Wesley will be informed by letter to the agreed upon “points of contact” within the Medical Center. (21 CFR §56.108(a)(1) and §56.109(e))

H. Modification Log

The IRB Office will maintain a Modification Log. Each study approved pending modification will be entered into the log. Once all appropriate revisions are made and received, the log will be signed and dated by the IRB Director. (Should

there be any question concerning appropriateness of any revision, the IRB Chair will be consulted.) Each month the signed studies in the Modification Log will be presented to the IRB at its meeting and attached to the meeting's minutes.

I. Suspension or Termination of IRB Approval

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the Code of Federal Regulations, the IRB's decision, conditions, or requirements or that has been associated with unexpected serious harm to subjects. Serious or continuing noncompliance with the determinations of the IRB may result in the IRB withdrawing approval for a study. Failure to provide a response in a timely manner to request of information for continuing review is considered cause for suspension or termination of IRB approval.

Termination of approval and suspensions for serious cause (not late continuing review report, unless it becomes a consistent problem) will be reported by the IRB Office to appropriate institutional officials, the FDA, and/or OHRP within seven days. 21 CFR §56.108(b)

J. Minimal Risk

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The IRB alone reserves the right to define which protocols are minimal risk, and this definition will ordinarily occur in the course of a full IRB meeting unless the protocol meets all the specific criteria for expedited review. (21 CFR §56.102(i))

K. Eligibility for Exempt Status

These six exemption categories do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization.

1. Exemption Categories: Research activities, in which the only involvement of human subjects will be in one or more of the following categories, are exempt from the requirement for IRB review:
   a. Research conducted in established or commonly accepted educational settings, involving normal education practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. (45 CFR §46.101(b)(i) and Footnote 1)
   b. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
      (i) information is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
      (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability, or be damaging to the subjects' financial standing, employability, or reputation. RESEARCH DOES NOT APPLY TO RESEARCH WITH CHILDREN, EXCEPT FOR RESEARCH INVOLVING OBSERVATIONS OF PUBLIC BEHAVIOR WHEN

THE INVESTIGATOR(S) DO NOT PARTICIPATE IN THE ACTIVITIES BEING OBSERVED. (45 CFR §46.101(b)(2) and 45 CFR §46.401(b))

c. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph b(ii) of this section, if
   (i) the human subjects are elected or appointed public officials or candidates for public office; or
   (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. (45 CFR §46.101(b)(3))

d. Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available, or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. (45 CFR §46.101(b)(4))

e. Research and demonstration projects, which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs. (45 CFR §46.101(b)(5))

f. Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed, or (ii) if food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration, or approved by the Environmental Protection Agency, or the Food Safety and Inspection Service of the U.S. Department of Agriculture. (45 CFR §46.101(b)(6) and 21 CFR §56.104(d))

2. Procedures for Reviewing Potentially Exempt Research:

a. All research proposals involving humans or human biological specimens must be submitted in the form of several paragraphs discussing the research or by using the application form for new projects to the WMREF office for review by the WMREF IRB.

b. A screening form listing the six potentially exempt research categories [according to 45 CFR 46.101(b)] may be completed by any investigator submitting a proposal, wherein the investigator may petition to have his/her proposal reviewed according to WMREF IRB Policies and Procedures as a "potentially exempt" protocol.

c. The IRB may authorize one or more specifically named persons to triage submitted proposals and nominate those which appear to meet criteria for the "potentially exempt" category as defined by section IV, J., of the WMREF IRB Policies and Procedures (above).

d. A review procedure may be carried out by the IRB Chairperson or by an experienced IRB member designated by the Chairperson. In reviewing eligibility for the "exempt" category, the reviewer may exercise all of the authorities of the IRB except that the reviewer may not disapprove the

research. A research activity may be disapproved only after review in accordance with the non-expedited procedure.

e. If the reviewer decides that the submitted proposal meets criteria for one of the six "potentially exempt" categories and does not involve other non-exempt research activity, the reviewer must document which of six categories applies with a brief note about the correspondence between the submitted proposal and the "potentially exempt" category. This record must be signed and dated by the reviewer.

f. When a submitted proposal is found to be "exempt" according to these procedures, the IRB Director shall notify the investigator, indicating that further IRB review is not required in this case. The submitted proposal will remain on file in the WMREF Office. When a submitted proposal is not found to be "exempt," the protocol will be submitted to the full IRB for review according to usual policies and procedures.

g. Exemption from Review will be used only for two reasons,
   1) To improve the efficacy of the IRB, or
   2) At the request of the investigator, who must designate at the time of the request which exempt category is being met by the research proposal.

L. "Identifiers" as related to Exempt-Eligible Research

Two of the six categories for "exempt" status (1.b. and 1.d. under J on page13) require the IRB to determine whether "the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects."

"Identifiers" refer to names, unique identification numbers, or codes that could conceivably be traced back to names. "Identifiers" also refer to unique identifying characteristics that might reasonably contribute to the discovery of a subject's name. Many investigators believe that by substituting codes for names or patient identification numbers, they effectively remove identifiers. The WMREF IRB does not subscribe to this belief. If one or more "decoding" keys exist (anywhere) which might allow the investigator to decipher anonymous subject codes, in order to obtain the identity of a subject in a clinical-emergency situation, for example, WMREF IRB policy considers this database to be one maintained with "identifiers."

Since investigators are often in direct contact with subjects, the issue of "identifiers" hinges on how investigators record their data. Neither the central database for a study, nor the investigator, nor his/her research associates, may retain any identifiers if a study is to be considered "exempt-eligible."

When the investigator proposes to obtain and record data with no "identifiers" or "links" to other identifiers, the case for straightforward exemption is likely. When, however, the investigator plans to obtain and record data with “identifiers" or "links" as a matter of practical necessity, this investigator must also present a plan to systematically destroy all "identifiers" and "links" as soon as possible (always prior to data analysis), if this investigator wants to make a case for exemption eligibility.

Several types of procedures and written assurances for the IRB might lead an IRB member to decide that an investigator could collect data forms with identifying information, transfer the data to a central database without identifying information, and then destroy the data forms. These include:

1. The investigator makes a convincing case that there are scientific reasons to use data forms with identifying information in the initial phase;
2. The data forms with identifying information are handled and stored with extraordinary care;
3. The data forms with identifying information have a short life, and are stored only until the data can be transferred to a central database without identifying information;
4. The data forms with identifying information are systematically destroyed by the Principal Investigator himself/herself; and
5. The Principal Investigator assures the IRB that once the data forms are destroyed, no identifying links between subject and data provided remain in existence anywhere.

M. Eligibility for Expedited Review

Expedited Review will be used only for two reasons,

1) To improve the efficacy of the IRB, or
2) At the request of the investigator, who must designate at the time of the request which expedited category is being met by the research proposal.

The IRB may use the expedited review procedure to review either or both of the following categories. These two are the only categories wherein non-exempt proposed research need not be reviewed at convened IRB meetings.

1. Some or all of the research activities appearing on the list published by the Secretary, HHS, (itemized in the following paragraph) and judged by the reviewer(s) to involve no more than minimal risk, and/or
2. Minor changes in previously approved research during the period (of 365 days or less) for which approval is authorized.

Standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review – expedited or convened – utilized by the IRB.

The following is a list of research activities involving no more than minimal risk, if carried out through standard methods, according to federal regulations (63 FR 60364 - 60367; November 9, 1998). Activities listed should not be considered to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects. The categories in this list apply regardless of the age of the subjects, except as noted. The WMREF IRB will limit its use of the category "minimal risk" to the following eight examples:

2. Collection of blood samples by finger stick, heel stick, ear stick or venipuncture as follows:
   (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
   (b) from other adults and children (as defined in 45 CFR §46.402(a)), considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supr- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples:

(c) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
(d) Weighing or testing sensory acuity;
(e) Magnetic resonance imaging;
(f) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography;
(g) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

4. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis.)

5. Collection of data from voice, video, digital, or image recordings made for research purposes.

6. Research of individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

8. Continuing review of research previously approved by the convened IRB as follows: (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research related interventions; and (iii) the research remains active only for long-term follow up of subjects; or (b) where no subjects have been enrolled and no additional risks have been identified; or (c) where the remaining research activities are limited to data analysis.

9. Continuing review of research, not conducted under an investigational new drug application or an investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a

convened meeting that the research involves no more than minimal risk and no additional risks have been identified.

Minor changes in previously-approved research protocols include:

(1) changes to the literature review that do not contradict the original review or do not amplify potential risks;
(2) changes of single words or single phrases in the informed consent documents which do not alter the meaning of the informed consent process;
(3) subject recruitment numerical goals of ten percent or less;
(4) changes/corrections in pagination;
(5) changes in addresses, e-mails, or other contact information;
(6) Adding or deleting research staff with the exception of the principle investigator or sub-investigator;
(7) deleting a research funding source;
(8) name changes such as a change in sponsor, the change in a contact person's name, etc.,
(9) clinically insignificant changes in inclusion/exclusion criteria, so long as it is unlikely that changes in the definition of subgroups at risk (e.g., children, the economically disadvantaged, racial/ethnic subgroup composition) ensue;
(10) the deletion of specific assays or interview forms from a battery of previously-approved measures, so long as key intervention conditions are not altered;
(11) addition of reminder/appointment cards for follow-up study visits;
(12) changes in protocol for closure to subject recruitment. All subjects must be either in follow-up or have completed the study. The continuing review date remains the same;
(13) IRB Office may send letters/memos of acknowledgement for the following situations:
   (a) IRB acknowledgement of safety report receipt.
   (b) IRB acknowledgement of other sponsor-generated information that requires verification of IRB receipt (e.g. study closure).

An expedited review procedure may be carried out by the IRB Chair or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authority of the IRB except that the reviewers may not disapprove the research. All submitted proposals that fail to meet the criteria for expedited review must be submitted for review by the entire IRB. A research activity may be disapproved only after review in accordance with the nonexpedited procedure.

The expedited review process will not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing (including genetic testing,) unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

At each IRB meeting, every IRB member will be provided with a complete list of all proposed research approved by means of the expedited review procedure since the preceding IRB meeting. The intent is to keep all IRB members advised of research proposals and amendments which have been approved by means of the Expedited Review

procedure, and to provide them with an opportunity to discuss, raise questions, or object to specific expedited review actions. (21 CFR §56.108(a)(1) and §56.110(a-c))

N. Inclusion of Children/Minors in Human Subjects Research Sponsored by NIH

Children, or persons under the age of 21, must be included in all human subjects research conducted or supported by NIH unless there are scientific and ethical reasons not to include them (NIH Policy and Guidelines on the inclusion of children as participants in research involving human subjects, March 6, 1998). This requirement does not extend to projects sponsored by federal agencies other than NIH, and does not apply to projects that are not funded by NIH.

Submitted proposals for NIH-sponsored research involving human subjects must include a description of plans for including children. If children are to be excluded from the research protocol, the proposal must present a justification for this exclusion. Thus a section titled "Participation of Children" should routinely appear. Where children are to be included, the proposal should include a rationale for selecting or excluding a specific age range of children, a description of the expertise of the investigative team for dealing with children at the ages cited, the appropriateness of available facilities to accommodate children, and the inclusion of a sufficient number of children to culminate in a statistically meaningful analysis for purposes of the study hypotheses. Where children are to be excluded, the investigator should provide an explanation of the reasons for excluding children as participants.

Children should be included in all research involving human subjects research conducted or supported by NIH unless one or more of the following exclusionary circumstances has been fully justified:

1. The research topic under consideration is irrelevant to children.

2. There are regulations barring the inclusion of children in the research. For example, federal regulations for the protection of human subjects allow consenting adults to accept a higher level of risk than is permitted for children.

3. The knowledge being pursued in the research is already available for children, or will be obtained from a different ongoing study, so an additional study is redundant. The existence of other studies justifying an exclusion decision should be provided by the investigator.

4. A separate, age-specific study in children is warranted and preferable. For example, when a condition being studied is rarer in children than in adults, an extraordinary effort might be required to include children. When a particular condition is already the subject of a national pediatric disease research network, it might be difficult or counter-productive to include child cases in a proposed adult study. Study hypotheses might not apply evenly to adult and child subjects because different cognitive, developmental, or disease stages or different age-related metabolic processes are thought to operate; but consideration should still be given to taking these differences into account in the study design by expanding the hypotheses or interventions being tested to allow children to be included.

5. Adult studies yield insufficient data for judging potential risk in children. This situation might constitute justification for a research objective to obtain sufficient adult data to make this same judgment. While children should usually not be the initial group to be involved in research studies, the nature and seriousness of the illness in some instances may warrant their participation earlier based on a careful risk-benefit analysis.
6. A study is designed to collect additional data on subjects who were previously enrolled as adult participants, so the original study never included data on children.

3. Other special cases justified by the investigator and found acceptable to the IRB.

O. Inclusion of Children/Minors in Human Subjects Research Sponsored by the FDA

FDA-sponsored research with children as subjects is to be handled in a similar manner to the way it is handled in NIH sponsored research. (FR Vol. 66, No. 79, 4/24/01, pages 20589-20600 and 21 CFR Subpart D) The similarities include the four categories of research and the documentation for that research to take place, including permission and assent. The major differences are due to FDA-related research involving investigational drugs, devices, and biologicals and proprietary study sponsors. (See also Checklist for IRB Approval of Pediatric Research in Appendix.)

P. Administrative Approval/Disapproval of Research

Human subjects research that has been approved by the IRB may be subject to further appropriate review and approval or disapproval by officials of the participating institution. However, those officials may not approve the research if it has not been approved by the IRB.
(21 CFR §56.112)

Q. Primary Reviewer System

The IRB Chairperson may designate IRB reviewers for each protocol on the agenda. The designated reviewer will receive a copy of the investigator's summary, consent documents, the protocol and all supporting documentation. All other members will receive the investigator's summary, consent documents, and, as applicable, other miscellaneous supporting documents. All other documents will be available at the meeting. The IRB Chairperson, Vice-Chairs, or Director may also serve as Contingency reviewers for each protocol. During the course of the regularly scheduled IRB meeting, the designated IRB reviewer shall, unless already done so by the principal investigator, summarize the assigned protocol for the benefit of the remainder of the IRB. This reviewer takes primary responsibility for reviewing the adequacy of human subjects protection. In the absence of the designated IRB reviewer, a Contingency reviewer may fulfill the responsibilities of the designated reviewer.

The IRB Chair or IRB Staff will assign a reviewer for each new study. The IRB Office will note those reviewers on the meeting agenda. While each IRB member is expected to participate in reviewing each new research study, in many cases the primary reviewer will have the only copy of the Investigator's Brochure.

Guidelines for the Primary Review

1. Carefully review the research project, using the IRB Consent Form Checklist to review the informed consent document for completeness. (A copy of the checklist can be found in the Appendix.) Some, but not all, important points to clarify for the Board are:
    a. What is the purpose of the research?
    b. What is experimental versus what is treatment?
    c. Are any standard therapies being withheld?
    d. What are the risks and benefits of the study?
    e. Are the risks in the protocol and/or risks from prior investigations included in the consent?
    f. Is the research appropriate for the subject population?
    g. Is a vulnerable population to be studied, and, if so, are there safeguards?
2. Reviewers are encouraged to contact the investigator with any questions or recommendations as soon as they are noted. Changes should be sent to both the primary reviewer for verification and to the IRB Office for delivery to members prior to the IRB meeting.
3. If the primary reviewer or investigator feels that the research presents problems or issues which must be resolved before it is presented to the IRB, the IRB Office should be notified.
4. If the primary reviewer does not feel that he/she can work with the investigator to resolve the problems/issues, notify the IRB Office. Another IRB member may work with the assigned reviewer or handle the study for him/her.
5. If a primary reviewer finds that he/she cannot attend the IRB meeting, he/she is asked to complete their review and use one of the following methods of giving their review information to the Board:
    a. Send a written summary on the reviewer's sheet to the IRB Office. The information may also be faxed or emailed.
    b. Call the IRB Office and discuss the review with the IRB Chair or IRB Director who can provide the information at the meeting.
    c. Call the IRB Office in enough time that an alternate Primary Reviewer can be assigned to that study.
6. If the primary reviewer is detained and cannot provide a report or information on their review, the Board may choose one of the following courses of action:
    a. Reschedule the study for review at the next meeting.
    b. Do an in-depth review at the current meeting, utilizing the attending members to determine the study status.
    c. Have a Contingency reviewer step in for the primary reviewer.

R. Secondary Reviewer System

A non-scientific member of the IRB may be designated by the IRB Chairperson or IRB Staff as the secondary reviewer for each protocol on the agenda. The secondary reviewer will receive the same materials as listed above for members who are not the-primary reviewer. The primary task of the secondary reviewer during the course of a regularly-scheduled IRB meeting is to serve as a second opinion on the research being considered. It is also the task of the secondary reviewer to bring up any area(s) found to be unclear, especially as it/they pertain(s) to the informed consent document. The secondary reviewer is also asked to consider the study as it relates to the community served by this IRB.

S. Relationship to the WMREF Scientific Review Committee

The WMREF Scientific Review Committee is responsible for determining the scientific merit of locally-developed studies and any other studies coming to the IRB Office that are not government- or industry-sponsored. The committee has the authority to recommend changes in proposed research to strengthen the scientific validity of the proposal. The Scientific Review Committee is made up of scientists in various areas of expertise. It must review and approve applicable studies before they can be brought before the IRB for review. The WMREF IRB has responsibility for the scientific merit of all studies it reviews, independent of study source. (The Scientific Review Committee Investigator Checklist for Submitting Research Protocols is in the Appendix.) (FIS Appendix H, IX, C)

At one time, the Scientific Review Committee was the only way scientific merit was acknowledged by the WMREF IRB. Since the institution of the Memorandum of Understanding (MOU) between UKSM-W, Wesley Medical Center, and the WMREF, another means of obtaining approval for scientific merit exists. Only for those studies meeting the MOU criteria, the scientific merit determination may be determined by one of two means:

1. Approval through the WMREF Scientific Review Committee, OR
2. Approval through UKSM-W, where two pages are submitted with the department chair or designee signature for scientific merit. These two pages include the overall scientific merit and the checkoff list that follows it. In this event, the Chair of the WMREF Review Committee will verify that the study meets the SRC criteria and may waive full SRC review.

A third means of obtaining scientific review approval through WMREF is a waiver given by the Chair of the Scientific Review Committee, who may request evaluation by other members of the committee, for very simple research such as a case series or survey study.

The Scientific Review Committee meets the first Thursday of the month. In order to be included on the upcoming meeting agenda, all required materials must be turned in to the IRB Office no later than two weeks prior to the meeting. Any studies submitted later will be placed on the agenda for the next month's meeting. Investigators are required to attend the meeting to present their research plan and answer questions. Investigators will be notified of meeting date, place, and time beforehand.

When the SRC writes a letter to the Principal Investigator requiring modifications after r eview, the investigator has 60 days from the date of the letter to submit the modifications to the WMREF Office. Investigators may request an extension of this time period prior to the end of the 60 days. An explanation of circumstances justifying the extension must accompany the request. Failure to do so will result in the need to resubmit the project.

V. IRB REVIEW OF CONSENT DOCUMENTS AND PROCEDURES

A. Informed Consent Process

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The only exceptions to the informed consent process requirement are: (a) individual studies which have been certified as "Exempt" from IRB review by the IRB Chair, Vice-Chair, or Director; and (b) individual studies where the WMREF IRB has waived the requirement to obtain all or elements of informed consent as certified by the WMREF Office.

An investigator shall seek informed consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any absolving language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.
(45 CFR §46.116)

Approved consent forms and (if separate) HIPAA Authorizations will be marked with the date of approval by the WMREF IRB. The IRB Office may choose the most efficient and effective manner of accomplishing this, and may include a stamping process, marking in the header and/or footer of the document(s), and/or requiring a fresh version of the document(s) from the investigator(s) at the time of continuing review and/or the time of changes to the document(s).

B. Required Elements of Informed Consent

For all studies:

1. a statement that the study involves research,
2. an explanation of the purposes of the research,
3. the expected duration of the subject's participation,
4. a description of the procedures to be followed,
5. identification of any procedures which are experimental (i.e., procedures involving manipulation of the subject physically or psychologically),
6. a description of any reasonably foreseeable risks or discomforts to the subject,
7. a description of any benefits to the subject or to others which may reasonably be expected from the research,
8. a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, (including that the FDA and/or HHS OHRP may inspect the records, when appropriate)
9. an explanation of whom to contact for answers to pertinent questions about the research [the Principal Investigator], research subjects' rights [WMREF IRB Office], and whom to contact in the event of a research-related injury to the subject [Principal Investigator and/or Sponsor], and
10. a statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
(21 CFR §50.25(a) and 45 CFR §46.116)

For specific types of studies:

11. for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained,
12. for treatment studies, a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject, and
13. for treatment studies, clear distinction between procedures which are considered to represent "usual care" and those considered to represent "research interventions".

When appropriate, one or more of the following elements of information must also be provided to each subject:

14. a statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable,
15. anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent,
16. any additional costs to the subject that may result from participation in the research,
17. the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject,
18. a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject, and
19. the approximate number of subjects involved in the study.

(21 CFR §50.25(b))

The informed consent requirements in this policy do not preempt any applicable Federal, State, or local laws that require additional information to be disclosed in order for informed consent to be legally effective.

C. Documentation of Informed Consent (HHS 45 CFR §46.117; FDA 21 CFR §50.27**)**

Informed consent shall be documented by the use of a written consent form approved by the WMREF IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form. (HHS 45 CFR §46.117(a); FDA 21 CFR §50.27(a))

The only exceptions to the requirement for documentation of informed consent documentation requirement are:

(a) individual studies which have been certified as "Exempt" from IRB review by the WMREF IRB; and

(b) individual studies where the WMREF IRB has waived the requirement to obtain all or elements of informed consent as certified by the WMREF IRB.

The consent form must be either a written consent document or a short form written consent document. A written consent document according to HHS §46.117(b)(1) (FDA §50.27(b)(1)) is one that embodies the elements of informed consent required by 45 CFR 46.116 (FDA 21 CFR 50.25). This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

Alternatively, §46.117(b)(2) (§50.27(b)(2)) permits oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent required by §46.116 (§50.25) have been presented orally to the subject or the subject's legally authorized representative) and a WMREF IRB approved written summary of what is presented orally to the subject or the representative. When this method is used, a witness to the oral presentation is required, and the subject must be given copies of the short form document and the summary. Signatures shall be obtained as follows:

a) the short form itself is to be signed by the subject or the representative,
b) the witness shall sign both the short form and a copy of the summary, and
c) the person actually obtaining the consent shall sign a copy of the summary.

A copy of the WMREF IRB approved written summary shall be given to the subject or the representative, in addition to a copy of the short form.

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either (HHS 45 CFR §46.117(c); FDA 21 CFR 50.109(c)):

1. That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; (HHS 45 CFR §46.117(c)(1); No parallel FDA regulation exists)

OR

2. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. (45 CFR §46.117(c)(2) or 21 CFR 56.109(c)(1))

The FDA regulations do not contain a parallel regulation to 45 CFR 46.117(c)(1) regarding waiving the requirement for a signed consent form because the FDA does not regulate research in which "the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality."

In cases in which the documentation of informed consent requirement is waived, the WMREF IRB may require the investigator to provide subjects with a written statement regarding the research.(HHS 45 CFR 46.117; FDA 21 CFR 56.109(d)).

Investigators must use the copy of the informed consent document reviewed, approved, and dated with approval date by the WMREF IRB. Unstamped equivalents and altered versions (no matter how small the alteration) may never be employed unless the WMREF IRB grants an exception.

D. Requirements for Permission by Parents or Guardians and for Assent by Children

The WMREF IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived.
(45 CFR §46.408(a)

The WMREF IRB shall determine, in accordance with and to the extent that consent is required, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR §46.404 or §46.405 or 21 CFR §50.51 or §50.52 (i.e., *"Research not involving greater than minimal risk"* or *"Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.")*

Where research is covered by 45 CFR §46.406 or §46.407 or 21 CFR §50.53 or §50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child *("Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition " or "Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.* ")

In addition to the provisions for waiver of informed consent, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the

subjects (for example, neglected or abused children), it may waive the consent requirements, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition. 45 CFR §46.408(c)

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR §46.406/21 CFR §50.53 or 45 CFR §46.407/21 CFR §50.54 *("Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition " or "Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. ")* only if such research is:

1. related to their status as wards; OR
2. conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(45CFR §46.409(a))

In research with children who are wards of the State or any other agency, institution, or entity approved under 45 CFR §46.406/21 CFR §50.53 or 45 CFR §46.407/21 CFR §50.54, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.
(45 CFR §46.409(b)

Permission by parents or guardians shall be documented in accordance with and to the extent required for adult subjects. When the IRB determines that the assent of child subjects is required, it shall also determine whether and how assent must be documented.
(See also Checklist for IRB Approval of Pediatric Research in Appendix.)

E. Documenting Informed Consent with Illiterate Subjects

For the purposes of this document, illiterate will be defined as anyone who did not finish elementary school (6th grade) or anyone who cannot read or write.

When the investigator plans to target illiterate subjects for a study due to their lack of education or ability to read and/or write, a very simple, very basic document will be constructed for the subject to keep in his/her records. This document will outline, in the simplest manner possible, the basic information regarding the study in which he or she is being asked to participate.

When recruiting an illiterate subject for study participation, the Principal Investigator or other staff person must take pains to:

1. Ascertain that the study description is clear and simple enough for the potential subject to understand; and

2. Read the entire informed consent document to the potential subject, along with all other similar documentation;
3. Provide the potential subject with ample opportunity to ask questions and request clarification in an unhurried manner.

The Principal Investigator or other staff person must attach a typed memo to the informed consent document, noting that the subject is considered illiterate and all three of the above conditions have been fulfilled. The subject may sign the consent document in the appropriate place with his/her name or sign (i.e., an "X" is sufficient). The date, identity(ies), and signatures of all study personnel involved in this informed consent process should also be recorded. When a family member of the

subject is available and has participated in the informed consent process, that family member should also be noted and asked to sign as a witness to the process.

F. Translating Informed Consent Documents into Foreign Languages

No translated version of any informed consent document may be employed unless that translation has been reviewed, approved, stamped, and dated by the WMREF IRB. For every consent document submitted in a language other than English, the Principal Investigator is required to submit the following documentation:

1. a description of the medical translation qualifications of the translator, usually in the form of a curriculum vitae or resume; and
2. a letter from the translator, testifying to the completeness of the translation, or
3. a letter from each of two translators fluent in the language into which the document is translated, testifying to the completeness of the translation.

The IRB reserves the right to request that a translation be submitted to a translator of the IRB's choosing for a second opinion about the completeness of the translation, or to request translation by a translator with credentials more readily acceptable to the IRB.

G. Documenting Informed Consent with Non-English Speaking Subjects

1. Translated Consent Available

Before the study begins, the Principal Investigator should prepare a consent document in each of the subject languages he/she expects to encounter in the course of the study. Consent documents in languages other than English must be submitted to the WMREF IRB for review and approval before they can be deployed, according to the IRB policy for "Translating Informed Consent Documents into Foreign Languages."

The Principal Investigator must employ the services of a fluent translator to approach potential study participants who do not speak English. The translator must have a good grasp of the fundamentals of the research study and must be able to gauge the level of education and understanding of the potential subjects. The translator may not be a family member of the potential study participant. Both the staff member and the

translator engaged in the informed consent process with the subject should sign the consent documents. When a family member of the subject is available and has participated in the informed consent process, that family member should also be noted and asked to sign as a witness to the process.

2. Use of a Written Translation of the "Short Form" Document

The short form should generally be used only when the research involves no more than minimal risk to the subjects or, if more than minimal risk, the research presents the prospect of direct benefit to individual subjects.

If one or two potential subjects do not speak English, if the Principal Investigator had no way to anticipate the need for a translated consent document in a specific language, and if an appropriate translator is available, the Principal Investigator or other study personnel may allow the non-English speaking subject to be consented using a short form along with the approved consent. Short forms are available from the WMREF IRB in Arabic, Chinese, Dutch, French, Italian, Greek, Haitian Creole, Portuguese, Russian, Spanish, and Vietnamese. Versions in any other language must be preapproved by the WMREF IRB.

The "short form" attests that the elements of informed consent have been presented orally. When the "short form" is used to document informed consent, the consent process must include oral presentation of the English version of the consent form in a language understandable to the potential subject. An interpreter (preferably a medical interpreter) must be physically present to interpret, in the subject's language, the researcher's oral presentation of the English version of the consent form.

The consent process for enrolling subjects using the "short form" consent document is outlined in the following numbered information. **ALL** of the following requirements must be completed:

A. The Principal Investigator (or other member of the study staff with PI-delegated responsibility for obtaining informed consent) must present the WMREF IRB-approved English version of the consent form orally to the subject through a (medical) interpreter physically present and fluent in English and the language understandable to the subject;
B. The subject must be given a written translation of the 'short form' consent document in the language understandable to him/her to read;
C. The entire consent process must be witnessed by an individual who is fluent in both English and the language understandable to the subject. The interpreter may serve as the witness to the consent process (presentation of the information in the consent form in the language understandable to the subject and the opportunity to ask and receive answers to questions);
D. The WMREF IRB-approved English version of the consent form must be signed by the investigator obtaining informed consent **and** the witness to the consent process (see 3 above);
E. The written translation of the 'short form' must be signed by the subject **and** the witness to the consent process (see 3 above); and
F. The subject must be given signed copies of both the WMREF IRB-approved English version of the consent form **and** the written translation of the 'short form' consent document.

G. The original signed English version of the consent form with the original signed written translation of the '*short form*' document attached should be placed in the subject's research record. A copy of both forms should be placed in the subject's medical record, if the information is relevant to their medical care.

3. Post Initial Consent

Since informed consent is an ongoing process, issues relating to the subject's ability to understand and ask questions should continue to be considered throughout the study, and not just at the time of initial consent. For example, it is recommended to arrange for a (medical) interpreter to be available at subsequent study visits to ensure that subjects have an opportunity to ask questions and receive relevant study information.

Section V G References:
21 CFR 50.25
21 CFR 56.109(b)
FDA: A Guide to Informed Consent – Frequently Asked Questions, VII, #51
OHRP Memorandum: Obtaining and Documenting Informed Consent of Subjects Who Do Not Speak English, 11/09/95

H. Waiver of Informed Consent

Under certain circumstances specified in the Federal regulations, the IRB may approve a consent procedure which does not include some or all of the elements of informed consent, or may waive the requirements for obtaining informed consent. To do so, the IRB must find and document that:

- the research involves no more than minimal risk to subjects;
- the waiver will not adversely affect the rights and welfare of subjects;
- the research could not practicably* be carried out without the waiver; and
- whenever appropriate, the subjects will be debriefed – provided with additional pertinent information – after they have participated in the study.

(45 CFR §46.116.(d))

*"Practicable" is not an inconvenience or increase in time or expense to the investigator or investigation, rather it is for instances in which the additional cost would make the research prohibitively expensive or where the identification and contact of thousands of potentialsubjects, while not impossible, may not be feasible for the anticipated results of the study.

NOTE – FDA regulations do not provide for a waiver of consent, except in emergency situations. See section VI. B.

Waiver of Documentation of Consent

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds EITHER:

a. The only record linking the subject and the research would be the consent document and the principle risk would be potential harm resulting from a

breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research and the subject's wishes will govern.

OR

b. The research represents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

(45 CFR §46.117(c))

(FDA-regulated research will not ever fall into one of these two categories. See VI.B. for waiver of consent for research in the emergency setting.)

When the requirement for a signed consent is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research. All granted modifications will be reconsidered as a function of continuing or annual review.

I. THE NCI CIRB INDEPENDENT REVIEW MODEL: Local IRB Responsibilities

The NCI Central Institutional Review Board (CIRB) Initiative includes the establishment of the Cancer Prevention and Control (CPC) CIRB, extending the benefits of centralized review to investigators participating in clinical trials sponsored by the Division of Cancer Prevention (DCP).

The CPC CIRB (a NCI CIRB) reviews studies developed by the NCI Community Oncology Research Program (NCORP) and the Consortia for Early Phase Trials Program.

The National Cancer Institute (NCI) Community Oncology Research Program (NCORP) is a national network of cancer care investigators, providers, academia, and other organizations that care for diverse populations in health systems. The local NCORP is a Via Christi Hospitals, Inc., / Ascension affiliated program.

Based at Via Christi Hospital St. Francis, the Wichita NCORP is sponsored and funded by the National Cancer Institute and is named the signatory institution in the NCI CIRB Independent Review Model. Via Christi Cancer Institute manages the grant funding for Wichita NCI Community Oncology Research Program (NCORP), which brings the latest cancer research to Kansas.

The following Local IRB Responsibilities is based on the premise that the CPC CIRB's primary function is IRB review of adult and pediatric Cooperative Group research studies and that the signatory institution's primary function is consideration of local context and oversight of local performance of these studies. The signatory institution decides on a study- by-study basis whether to accept the NCI CIRB as the IRB of record for a particular study or to request IRB Full Board review through a local IRB.

Of particular importance, the NCI CIRB does not serve as the Privacy Board for research. The local IRB serves as the Privacy Board for research that takes place at a local affiliate institution, either as a component institution, or as an affiliate institution.

CPC CIRB (a NCI CIRB) / Signatory Institution Responsibilities:

The responsibilities of the CPC CIRB and the Signatory Institution are detailed in the Authorization Agreement/Division of Responsibilities located at the following URL: https://ncicirb.org/cirb/documents/AA_DofR.doc. The Authorization Agreement is signed by the Signatory Institution's Signatory Official and the Signatory Official for the CIRB during enrollment of the Signatory Institution and is required in order for the Signatory Institution to participate in the CPC CIRB.

Affiliate Institutions are defined by the CIRB as meeting all of the following criteria:

- The local context considerations of the Affiliate Institution are the same as the Signatory Institution.
- The boilerplate language and institutional requirements of the Affiliate Institution are the same as the Signatory Institution; and
- The conduct of research at the Affiliate Institution is monitored by the same office as the Signatory Institution.

The responsibilities of the affiliate institution's IRB includes, but is not limited to:

1) Intake new NCORP submission documents, to include but is not limited to, the Central IRB Utilization Form, the Model Consent, the Modified Consent to incorporate boilerplate language, the research protocol, the CIRB Approval of the Study-Specific Worksheet About Local Context, the stand-alone HIPAA Request for Authorization of Protected Health Information research form and the CIRB Initial Approval Application.
2) Log new study into IRB+ tracking database, review documents for boilerplate language insertions, collect NCI CIRB documents and maintain records for each NCI CIRB approved study opened at the affiliate institution by the signatory institution.
3) Perform a review of proposed site-specific changes to be made, before, concurrently, or shortly after, submission to the NCI CIRB. Any associated fees will be the responsibility of the NCORP.
4) The IRB will review the submitted documents and advise the NCORP of any questions or issues or request additional study documents, if needed. Any revisions involving any of the submitted documents will be submitted to the IRB.
5) If there are no issues to be resolved, or once any issues are resolved, the IRB will provide notice to NCORP that no further information is needed and no additional concerns were identified.
6) The local IRB will be informed through a consent agenda entry of each NCI CIRB approved research study opened at the affiliate institution at the next fully convened IRB meeting.
7) Act as corresponding agent and document repository for any documents that NCORP might submit related to a specific study and alert the affiliate institution, if notified, when NCORP investigates, manages, and provides notification to the NCI CIRB of any study-specific incidence, experience, or outcome that appears to rise to the level of serious or continuing investigator noncompliance.
8) Obtain local IRB approval of changes to the boilerplate language prior to submitting to the NCI CIRB and prior to incorporation to any consent form.
9) Maintain a regulatory file for each study under CIRB purview as per local institution and sponsor policy.
10) The local IRB may not conduct full board review of any study enrolling prisoners, since this local IRB is not constituted to review studies enrolling prisoners.
11) Serving as the Privacy Board for Research for the affiliate institution, review and provide expedited approval of a separate, stand-alone HIPAA Request for Authorization of Protected Health Information research form.
12) In addition, the local IRB serving as the Privacy Board for Research, will expect to receive a revised HIPAA Authorization Form should future study revisions precipitate changes to the approved HIPAA Authorization Form.
13) Receive notification from the signatory institution when the study closes at the affiliate institution.
14) Send notification to the affiliate institution's Privacy Officer of the action to open an NCI CIRB approved research study at the affiliate institution.

15) Maintain an OHRP-approved Assurance for human subjects research and an OHRP IRB registration number;

16) Maintain a human subjects protection program compliant with 45 CFR 46 and 21 CFR 50 and 21 CFR 56.

17) Maintain compliance with state, local, or institutional requirements related to the protection of human subjects.

Further Delineation of Responsibilities by Topic:

Assent (for pediatric trials):

The CIRB makes the determination whether assent of the child is required. Local institutional policy regarding whether and how to document assent is provided as part of the local context considerations.

HIPAA:

Compliance with HIPAA regulations is considered an institutional requirement and remains the purview of the local institution.

Including HIPAA Authorization language as part of boilerplate language is permitted. The CIRB does not approve the HIPAA Authorization language, as it does not function as a Privacy Board however, the CIRB will accept HIPAA Authorization language when submitted as part of the boilerplate.

Incompetent Adults:

The CIRB determines whether individuals with impaired decision-making capacity as a category are eligible for a study. The local institution provides the details regarding state law and institutional policy regarding the authority of legal guardians to consent to research, as well as documentation of proxy consent as part of the local context considerations.

Prisoners:

The CIRB and this local IRB is not constituted to review studies eligible for prisoners, per 45 CFR 46 Subpart C, so cannot be the IRB of Record if the local investigator wants to enroll a prisoner or if a study participant becomes incarcerated during the course of the study. If the local investigator wants to enroll prisoners on a particular study, or if a study participant becomes incarcerated during the course of the study, the a local IRB constituted to review studies eligible for prisoners, per 45 CFR 46 Subpart C must conduct a full board review of that study per Federal regulations.

Other Committee Reviews:

The CIRB's review is designed to meet the requirements for review by an Institutional Review Board (IRB). Requirements for review by other committees such as a Radiation Safety Committee or Institutional Biosafety Committee are the responsibility of the local institution.

J. Memorandum of Understanding with University of Kansas School of Medicine – Wichita and Wesley Medical Center

Minimal Risk Research

In early 2009, WMREF, Wesley Medical Center, and the University of Kansas School of Medicine – Wichita (UKSM-W) signed a memorandum of understanding. This memorandum allows investigators doing minimal risk research that must be reviewed by both the KU Humans Subjects Committee and the WMREF Institutional Review Board to use one set of common forms. There is a set of forms for retrospective research and a set for prospective research. An original submission form with all required information and documentation must be submitted to each IRB/HSC. However, in cooperation, only one IRB will review the research. If the research involves Wesley Medical Center patients, employees, records, and/or facilities, the WMREF IRB will do the majority of the reviewing process.

Forms for these cooperative submissions can be found on the KU Compliance Website, which is: http://wichita.kumc.edu/afs/compliance/forms2.html. A listing of additional materials required by WMREF can be found in a table on that site. Any additional requirements will be listed on the WMREF website under "If Using KU Forms" at: http://www.wichitamedicalresearch.org/institutional.shtml#forms . No additional information is required beyond that which is required when applying directly to WMREF for IRB approval.

VI. IRB REVIEWS RELATING TO THE (HIPAA) PRIVACY ACT – THE IRB ACTING AS A PRIVACY BOARD

A. IRB as a Privacy Board

The WMREF IRB handles the responsibilities given to either an IRB or Privacy Board in the HIPAA Privacy regulations, as found in 45 CFR §160 and §164. In addition, it will review for approval Authorizations to Use and Disclose Protected Health Information (PHI) for Research Purposes.

1. The IRB will act on the part of the Covered Entity to review Authorizations for Use and Disclosure of Protected Health Information for Research. Actions of the IRB may include approving, requiring modification to obtain approval, and approving alteration to or waiver, in whole or in part, the individual authorization required by §164.508 for use or disclosure of protected health information.(45 CFR 164.512(i) and (i)(1)(i))
2. A stand-alone authorization (as opposed to one combined with the informed consent document) may be approved by expedited review by the IRB Chair and/or the IRB Chair's designee. Authorizations combined with the informed consent will undergo full board review at a convened meeting, unless the study is eligible for expedited review.
3. IRB review of an authorization will include all of the elements required by the Privacy Rule and listed in the WMREF IRB Checklist for Authorization to Use and Disclose Protected Health Information for Research Purposes. These are taken directly from the regulations found in 45 CFR 164.508(c).
   a. A valid authorization must contain at least the following core elements, as well as required statements.

Core elements must include at least the following elements:

(i) A description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion. (45 CFR 164.508(c)(1)(i))

(ii) The name or other specific identification of the person(s), or class of persons, authorized to make the requested use or disclosure. (45 CFR 164.508(c)(1)(ii))

(iii) The name or other specific identification of the person(s), or class of persons, to whom the covered entity may make the requested use or disclosure. (45 CFR 164.508(c)(1)(iii))

(iv) A description of each purpose of the requested use or disclosure. The statement "at the request of the individual" is a sufficient description of the purpose when an individual initiates the authorization and does not, or elects not to, provide a statement of purpose. (45 CFR 164.508(c)(1)(iv))

(v) An expiration date or an expiration event that relates to the individual or the purpose of the use or disclosure. The statement "end of research study," "none," or similar language is sufficient if the authorization is for a use or disclosure of protected health information for research, including for the covered entity to use or disclose protected health information for the creation and maintenance of a research database or research repository. (45 CFR 164.508(c)(1)(v))

(vi) Signature of the individual and date. If the authorization is signed by a personal representative of the individual, a description of such representative's authority to act for the individual must also be provided. (45 CFR 164.508(c)(1)(vi))

Required statements. In addition to the core elements, the authorization must contain statements adequate to place the individual on notice of all of the following:

(i) The individual's right to revoke the authorization in writing, and either: (45 CFR 164.508(c)(2)(i))
(A). The exceptions to the right to revoke and a description of how the individual may revoke the authorization (45 CFR 164.508(c)(2)(i)(A);
OR
(B). To the extent that the information in (c)(2)(i)(A) above is included in the covered entity's Notice of Privacy Practices as required by 45 CFR 164.520. (45 CFR 164.508(c)(2)(i)(B))

(ii) The ability or inability to condition treatment, payment, enrollment or eligibility for benefits on the authorization by stating either (45 CFR 164.508(c)(2)(ii):
(A) The covered entity may not condition treatment, payment, enrollment or eligibility for benefits on whether the individual signs the authorization, except a covered health care provider may condition the provision of research- related treatment on provision of an authorization for the use or disclosure of protected health information for research (45 CFR 164.508(b)(4)(i)) & (45 CFR 164.508(c)(2)(ii)(A));
OR
(B) The consequences to the individual of a refusal to sign the authorization when, except in accordance with the regulation that a covered health care provider may condition the provision of research-related treatment on provision of an authorization for the use or disclosure of protected health information for research, the covered entity can condition treatment, enrollment in the health plan, or eligibility for benefits on failure to obtain such authorization. (45 CFR 164.508(b)(4)(i)) & (45 CFR 164.508(c)(2)(ii)(B))

(iii) The potential for information disclosed pursuant to the authorization to be subject to re-disclosure by the recipient and no longer protected by the Privacy Rule. (45 CFR 164.508(c)(2)(iii))

Plain language requirement. The authorization must be written in plain language. (45 CFR 164.508(c)(3)

Copy to the individual. If a covered entity seeks an authorization from an individual for a use or disclosure of protected health information, the covered entity must provide the individual with a copy of the signed authorization. (45 CFR 164.508(c)(4)

B. Review Activities

The Primary Reviewer for a new study will receive the stand-alone authorization, if there is one, in addition to all other items listed in Section (X)(e)(2) of this document. The authorization will be reviewed for completeness using the approved Authorization Checklist, whether the authorization is separate or part of the informed consent document.

The IRB, serving as the covered entities' privacy board for research, must review the authorization at convened meetings at which a majority of the members are present

and a majority of the members present voting to approve the authorization, including at least one member who is not affiliated with the covered entity, not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any of such entities unless the privacy board elects to use an expedited review procedure. (45 CFR §164.512(i)(1)(i)(B)(2)) and (45 CFR §164.512(i)(2)(iv)(B))

A proposal may be reviewed by expedited review procedures if the research involves no more than minimal risk to the privacy of the individuals who are the subject of the protected health information for which use or disclosure is being sought. The IRB Chair or his/her designee(s) may carry out the expedited review. (45 CFR 164.512 (i)(2)(iv)(C)

C. Waiver of Authorization

1. The Investigator must submit a HIPAA IRB Application for Waiver of Authorization of Use and Disclosure of PHI in order to request a waiver of authorization.

2. In order to approve a waiver or alteration, the IRB must determine the following criteria are satisfied: (45 CFR 164.512(i)(2)(ii)(A)(1-3))
    a. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements;
        i. An adequate plan to protect the identifiers from improper use and disclosure;
        ii. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
        iii. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by the HIPAA Privacy Rule;
    b. The research could not practicably be conducted without the waiver or alteration; and (45 CFR 164.512(i)(2)(ii)(B)
    c. The research could not practicably be conducted without access to and use of the protected health information. (45 CFR 164.512(i)(2)(ii)(C)
3. Records reviewed through a waiver of authorization must have an accounting of the disclosure per 45 CFR 164.528.

D. Documentation of Waiver Approval

The IRB will document the items a – c above, and in addition, identify the IRB and date alteration or waiver of authorization was approved, a brief description of the protected health information determined to be necessary for the research, a statement of whether convened meeting or expedited procedures were followed, and complete the document with a signature of the Chair or his/her designee(s). A WMREF IRB form has been provided

through the WMREF website for this use. (45 CFR §164.512(i)(2)

E. Reviews Preparatory to Research

The IRB may approve reviews preparatory to research under the following conditions agreed to by the investigator:

1. Use or disclosure is sought solely to review protected health information as necessary to prepare a research protocol or for similar purposes preparatory to research;
2. No protected health information is to be removed from the covered entity (such as Wesley Medical Center) by the researcher in the course of the review; and
3. The protected health information for which use or access is sought is necessary for research purposes. (45 CFR 164.512(i)(ii)

Reviews preparatory to research must have an accounting of the disclosure per 45 CFR 164.528.

F. Research on Decedent's Information

Research on Decedent's information does not have to go through the IRB/Privacy Board. The investigator should provide to the covered entity the following information:

1. Representation that the use or disclosure is sought solely for research on the protected health data of decedents;
2. Documentation, at the request of the covered entity, of the death of such individuals; and
3. Representation that the protected health information for which use or disclosure is sought is necessary for research purposes.

(45 CFR 164.512(i)(1)(iii)(A-B))

G. Limited Data Set/Data Use Agreement

A limited data set may be approved for use by the IRB acting as a Privacy Board for the purpose of research in conjunction with a Data Use Agreement (45 CFR 164.514(e)). A limited data set is protected health information that excludes the direct identifiers of the individual or of relatives, employers, or household members of the individual as listed in item (J). below, with a few notable exceptions. A limited data set may include five-digit zip codes, dates associated with the individual, such as birth date or date of procedure, and relevant medical information. A researcher may receive a Limited Data Set if the researcher negotiates a Data Use Agreement.

A Data Use Agreement between the covered entity (or the IRB acting on behalf of the covered entity for research purposes) and the limited data set recipient must:

1. Establish the permitted uses and disclosures of the information by the limited data set recipient. The data use agreement may not authorize the limited data set recipient to use or further disclose the information in a manner that would violate the requirements of the HIPAA Privacy Rule;
2. Establish who is permitted to use or receive the limited data set; and
3. Provide that the limited data set recipient will:
   a. Not use or further disclose the information other than as permitted by the data use agreement or as otherwise required by law;
   b. Use appropriate safeguards to prevent use or disclosure of the information other than as provided for by the data use agreement;

c. Report to the covered entity and IRB any use or disclosure of the information not provided for by its data use agreement of which it becomes aware;

d. Ensure that any agents, including a subcontractor, to whom it provides the limited data set agrees to the same restrictions and conditions that apply to the limited data set recipient with respect to such information;
and

e. Not identify the information or contact the individuals. (45 CFR 164.514(e)(4))

H. Accounting of Disclosures of Protected Health Information

An accounting of disclosure is required in certain situations. This includes when protected health information (PHI) is disclosed pursuant to a waiver of authorization and with identifiable limited data sets. It is not the responsibility of the IRB/Privacy Board to see that accounting of disclosure is done and doneproperly. This is the responsibility of the covered entity from which the PHI is disclosed. (45 CFR 164.528)

I. Transition Provisions

Transition provisions will be followed for all studies active prior to April 14, 2003, and remaining active as of that date. The details of these provisions are found in 45 CFR 46 164.532.

J. Identifiers as set forth in the HIPAA Privacy Rule

Identifiers include the following information of the individual or of relatives, employers, or household members of the individual:

1. Names;
2. All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and/or their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census:
   a. The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and
   b. The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of

   dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
4. Telephone numbers;
5. Fax numbers;
6. Electronic mail addresses;
7. Social security numbers;
8. Medical record numbers;
9. Health plan beneficiary numbers;
10. Account numbers;
11. Certificate/license numbers;
12. Vehicle identifiers and serial numbers, including license plate numbers,
13. Device identifiers and serial numbers,

14. Web Universal Resource Locators (URLs);
15. Internet Protocol (IP) address numbers;
16. Biometric identifiers, including finger and voice prints;
17. Full face photographic images and any comparable images; and
18. Any other unique identifying number, characteristic, or code, except as applies in 45 CFR 164.514(c) as it pertains to implementation specifications: Re-identification (45 CFR 164.514(b)(2)(i))

For Wesley-related research, also see WMC Administrative Policy.

VII. EMERGENCY USE OF INVESTIGATIONAL DRUGS/DEVICES/BIOLOGICS

A. Investigational Drugs, Devices, and Biologics for Persons NOT Enrolled in Clinical Trials

The use of investigational drugs, devices, and biologics for persons not enrolled in clinical trials always requires IRB approval, according to FDA regulations. Clinicians and investigators must apply to the WMREF IRB for this approval. Historically, these uses were incorrectly referred to as "compassionate use" or "compassionate approval." In fact, FDA regulations provide for different situations where the IRB can approve use of investigational drugs, devices, and biologics for persons not enrolled in clinical trials. These categories and procedures for accessing IRB approval are defined below:

1. **"Emergency management"**

Definition

- FDA regulations allow for use of a test article [i.e., investigational drug or device] in emergency situations without prior IRB approval.
- An "emergency situation" is defined as:
  a. life-threatening;
  b. no standard acceptable treatment is available; AND
  c. insufficient time to obtain IRB approval.
  (21 CFR §50.23(a))
- If the investigator intends subsequent use of the test article at the institution, every effort should be made either to sign on to the sponsor's protocol or to develop a protocol for future emergency use of the article at the institution, all with prior IRB approval.

Procedure

- Emergency use must be reported to the IRB in writing within five working days.(21 CFR §56.104(c) and 56.108(a)(3))
- The emergency use application must include a second opinion from a non-study affiliated second-party physician.
- All subsequent use of the test article must be reviewed by the IRB.(21 CFR §56.104(c) and 56.108(a)(3))
- The IRB Chairman must acknowledge receipt of the emergency use application within two working days. The application will be presented at the next IRB meeting and archived in the WMREF Office.
- Twelve months (or less as designated by the IRB) after approval, the investigator will make a report regarding the patient's progress and status.

2. **"Non-emergent single patient use"**

Definition

- This option allows a physician to obtain access to an investigational drug or device for the treatment of a single patient who otherwise does not qualify for a controlled clinical trial. The investigator must wait for IRB approval before initiating treatment.
- Usually, the patient is in a desperate situation and unresponsive to other therapies, or in a situation where no other approved or generally recognized treatment is available.
- There is usually little evidence that the proposed therapy is useful but the therapy may be plausible on theoretical grounds or anecdotes of success.

- This option permits only a single use of the test article for the treatment of one patient by one physician within the institution. If an investigator intends subsequent use of the test article at the institution, a research protocol or "treatment Investigational New Drug (IND) protocol" must be submitted to the IRB for review and approval.

Procedure

- Access may be gained either by petitioning the sponsor of an existing, approved treatment protocol (if an IND already exists), or by first obtaining the drug from the sponsor, and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment use.
- Once an IND access pathway has been established, the investigator must submit a request to the IRB in writing. Upon approval by the IRB Chairman, the information about the study will be presented at the next IRB meeting and archived in the WMREF Office.
- Twelve months (or earlier as determined by the IRB) after approval, the investigator will be contacted regarding the status of the subject. At that time the investigator must provide a report on the patient's progress and status for IRB review.

3. **Treatment Use of a Drug or Device**

As per 21 CFR §312.34 and 21 CFR §812.36, during the clinical investigation of a drug or device, it may be appropriate to use the drug or device in the treatment of patients not in the clinical trial, in accordance with a treatment IND or IDE (Investigational Device Exemption). The purpose of a treatment IND or IDE is to facilitate the availability of promising new drugs/devices to desperately ill patients as early in the drug/device development process as possible. The FDA may permit an investigational drug/device to be used for a treatment use under a treatment IND or IDE if:

a. The drug/device is intended to treat a serious or immediately life-threatening disease (defined as the stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment, e.g., advanced cases of AIDS, advanced congestive heart failure, advanced MS) (21 CFR§312.34(b)(i) and (b)(3)(B)(ii) and §812.36(b)(1));
b. There is no comparable or satisfactory alternative drug/device or other therapy available to treat that stage of the disease in the intended patient population (21 CFR §312.34(b)(ii) and §812.36(b)(2));
c. The drug/device is under investigation in a controlled clinical trial under an IND/IDE in effect for the trial, or all clinical trials have been completed (21 CFR§312.34(b)(iii) and §812.36(b)(3)); and
d. The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug/device with due diligence (21 CFR§312.34(b)(iv) and §812.36(b)(4)). Use of an investigational drug or device under a treatment IND must be approved by the IRB.

4. **Humanitarian Use Device (HUD) and Humanitarian Device Exemption (HDE)**

The FDA regulations provide for the approval of certain devices with disease states that affect patient populations in the United States of fewer than 4,000 per year. These are devices that have no alternative/satisfactory device on the market. Specifically, the purpose is to extent consistent with protection of the public health and safety and with ethical standards, to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are

manifested in fewer than 4,000 individuals in the United States per year. (21 CFR §814.100(a)) The FDA gives these devices approval under the HUD regulations with an assessment of safety and probable benefit.

Humanitarian use devices require a full IRB review (meeting of the full Board.)

a. No off label use is permitted for HUDs.
b. The IRB can approve use of HUDs for the labeled indication without any restrictions, on a case-by-case basis, or under a protocol.
c. The IRB may require an informed consent, but this is not mandatory in the regulations unless the HUD is the subject of a clinical investigation.
d. It is up to the IRB to decide if additional requirements (training, monitoring, credentialing, patient education, etc.) need to be met in order for an investigator to use the device.

B. Waiver of Consent for Investigational Drugs, Devices, and Biologics for Research in the Emergency Setting

The IRB may waive consent requirements for some or all patients in a study in the emergency setting.(21 CFR §56.109(c)(2) The following conditions must be met and documented:

1. Subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and collection of scientific evidence is necessary. (21 CFR §50.24(a)(1))
2. Obtaining informed consent is not feasible because: (21 CFR §50.24(a)(2))
    a. The medical condition precludes consent from the patient. (21 CFR §50.24(a)(2)(i))
    b. There is insufficient time to get consent from a legally authorized representative or the representative is unavailable. (21 CFR §50.24(a)(2)(ii))
    c. The prospective identity of likely subjects is not reasonable. (21CFR§50.24(a)(2)(iii))
3. There is the prospect of direct benefits to study subjects because: (21 CFR §50.24(a)(3))
    a. The patient is in a life-threatening situation that necessitates treatment, (21 CFR §50.24(a)(3)(i))
    b. Data supports the potential for direct benefit to individual subjects, (21 CFR §50.24(a)(3)(ii)) and
    c. The risk/benefit of both standard and proposed treatments are reasonable. (21 CFR §50.24(a)(3)(iii))
4. A waiver is needed to carry out the study. (21 CFR §50.24(a)(4))
5. The research plan defines a therapeutic window, during which the investigator will seek consent rather than starting without consent. A summary of efforts to obtain consent, written as they occur, will be given to the IRB at the time of continuing review. (21 CFR §50.24(a)(5))
6. The full board of the IRB has reviewed and approved the protocol, consent procedures, and consent document. The IRB has also reviewed and approved the procedures for a legally authorized representative or family member objection to consent. (21 CFR §50.24(a)(6))
7. Additional protections are taken, including at least: (21 CFR §50.24(a)(7))
    a. Consultation with community representatives (21 CFR §50.24(a)(7)(i))
    b. Public disclosure of plans, risks, and expected benefits, (21 CFR §50.24(a)(7)(ii))

c. Public disclosure of study results, (21 CFR §50.24(a)(7)(iii))
d. Assurance of the establishment of an independent Data Monitoring and Safety Board (21 CFR §50.24(a)(7)(iv))
e. A summary of objections of family members for IRB continuing review (21 CFR §50.24(b) and §50.24(a)(7)(v))

8. Ensure procedures are in place to inform at the earliest feasible opportunity of the subject's inclusion in the study and participation may be discontinued. Procedures are in place to inform the family that the subject was in the study if the subject dies.
9. A separate IND or IDE is required, even for marketed products.(21 CFR §50.24(d))

IRB disapproval must be documented in writing with the reason(s) for its determination and sent to the clinical investigator and the sponsor of the clinical investigation. (The sponsor then must promptly disclose the disapproval to the FDA, other investigators, and other IRBs reviewing the same investigational research.) (21 CFR §56.109(e) and §50.24(e))

The IRB shall provide in writing to the sponsor a copy of the information that has been publicly disclosed under 7b and 7c above. (21 CFR §56.109(g)
The IRB shall provide in writing to the investigator (and thereby the sponsor) when a 21 CFR §50.24 study is not approved and the reasons why. (21 CFR §109(e))

C. Investigational Drugs, Devices, and Biologics for Persons Entering a Second Institution

There will be patients who are participating in investigational studies approved by other IRBs (not the WMREF IRB), and who are admitted to Wesley Medical Center. When in doubt of whether an investigational agent(s) has been approved by the WMREF IRB, contact the WMREF IRB at 316-686-7172 (0800-1700 M-F). The WMREF IRB fax number is 316-687-0033. After WMREF IRB office hours, please proceed assuming that the patient is admitted on an investigational agent(s) (i.e. drug / biologic [defined by the FDA to include Allergenics, Blood & Blood Products, Cellular & Gene Therapy Products, Tissue & Tissue Products, Vaccines, Xenotransplantation] / device) from a second institution. These patients may bring their investigational agent(s) with them upon admission. In such cases, the following guidelines will be followed:

1. All personnel are to be on the alert for investigational agent(s) brought into the hospital. Clinical personnel are responsible for contacting the admitting physician, or the physician covering for the admitting physician, to determine whether the investigational agent(s) will be continued, if this determination has not already been done on admission.

2. The admitting physician, or the physician covering for the admitting physician, will decide whether to maintain the patient on the investigational agent(s) and inform the clinical investigator of the patient's admission. If continued, a physician's order shall be written by the admitting physician, or the physician covering for the admitting physician.

   Exception: If the admitting physician, or the physician covering for the admitting physician, does not have privileges to write orders for the investigational agent(s) per Wesley Medical Center Administrative

Policy, Section E, Policy 37, a physician with privileges must be consulted to write the investigational order.

The admitting physician, or the physician covering for the admitting physician, or designee (e.g., study coordinator, office representative) must place a copy of the:

a. Signed informed consent and protocol (or protocol's drug / biologic / device data section) on the patient's chart as soon as possible but no later than the next business day.
b. The WMC nurse or designee caring for the patient will scan the documents to the most appropriate department, the Pharmacy for drug agent(s) / the Ethics and Compliance Officer for biologic and device agent(s),_as soon as possible after receipt.

3. No investigational drug agent(s) may be administered or taken by a patient until the requirements of Wesley Medical Center Clinical Practice Medication Guidelines Section E, Policy 07, Patient's Own Parenteral Medication Brought to the Hospital and/or Section E, Policy 07.1, Patient's Own Non-Parenteral Medication Brought to the Hospital are met.

4. Once policy requirements have been met, the pharmacist / the Ethics and Compliance Officer will add or will instruct the proper department to add the investigational drug or agent(s) order to patient's medication profile with known interactions indicated. Interacting medications can be found in Pyxis Connect either in the investigational drug's protocol or as part of the physician's order for the investigational medication or agent(s).
   a. Known interactions will be programmed into the pharmacy computer system.
      NOTE: After hours contact a Pharmacy Department employee with the necessary Meditech training and privileges.
   b. In the event such person cannot be reached, the pharmacist will enter the 'NFROC' med item (non-chargeable) and perform a manual drug interaction check.
   c. Once the item is filed, any time pharmacists enter any new order for the patient, they will be alerted to perform a manual drug interaction check.

5. Exception: If the admitting physician, or the physician covering for the admitting physician, believes withholding the agent until the processes outlined above are completed will cause immediate hazard to the patient:
   a. The hazard must be documented by the admitting physician, or the physician covering for the admitting physician.
   b. Orders must be written for administration and observation for the investigational agent including type of drug or biologic or device, expected adverse effects, known drug interactions, and type and frequency of nursing observations necessary.
   c. The processes outlined above in VII.C.2., VII.C.3., and VII.C.4. must be implemented as soon as possible.

6. If neither step VII.C.2. nor step VII.C.5. as listed above have been completed, the pharmacist will follow the Chain of Command for Investigational Drug Use as outlined in Wesley Medical Center Clinical Practice Medication Guidelines,

Section E, Policy 35, Addendum 1, Chain of Command for Investigational Drug Use (revised 08/10/2011).

In the event Wesley Medical Center is responsible for a portion of the research protocol because a physician has been identified in the protocol as a sub-investigator and the WMREF IRB has not approved the study or agreed to accept the IRB of record as the responsible IRB, the pharmacist will contact the P&T Chair to request the principal investigator to submit the study to the WMREF IRB for review. If the P&T Chair does not receive a response from the principal investigator, the P&T Chair will contact the Chief Medical Officer who will contact the principal investigator.

7. It is the responsibility of the physician admitting the study participant to a second institution to contact the Principal Investigator of the patient's admission as well as any severe adverse or unanticipated events that occur while the participant is in the second institution. This is in keeping with the requirements for Events and/or Severe Adverse Event as noted in the regulations and in Section VIII. of these policies and procedures.

Section VII.C. References:

FDA: Use of Investigational Products When Subjects Enter a Second Institution, Guidance for IRBs and Clinical Investigators, www.fda.gov/regulatoryinformation/guidances/ucm126432.htm, page updated 10/18/2010

VIII. REVIEW OF SERIOUS UNANTICIPATED PROBLEMS AND/OR UNEXPECTED EVENTS

The Food and Drug Administration (FDA) requires investigators to report to the sponsor any adverse effect that may reasonably be regarded as caused by or probably caused by the drug (21 CFR §312.64(b)).

ALL DEATHS MUST BE REPORTED IMMEDIATELY TO THE IRB

Investigators are required to submit reports of events that are both serious and unanticipated to the WMREF IRB.

What MUST be reported to the IRB?

Unanticipated problems to be reported must meet ALL of the following three criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as IRB-approved research protocol and informed consent document, or product labeling and package inserts; and (b) the characteristics of the subject population being studied, such as the expected natural progression of any underlying disease, disorder, or condition of the subject;
2. related or possibly related (a reasonable possibility that the problem may have been caused by the research) to participation in the research; AND
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized. This includes a problem that;
    a. results in death;
    b. is life-threatening (places a subject at immediate risk of death from the event as it occurred);
    c. results in inpatient hospitalization or prolongation of existing hospitalization;
    d. results in a persistent or significant disability/incapacity;
    e. results in a congenital anomaly/birth defect; or
    f. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in a-e above.

Adverse events include any unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

An adverse event is also an unanticipated problem when ALL of the following criteria are met:

1. The adverse event is unexpected;
2. The adverse event is related or possibly related to participation in the research; and

3. The adverse event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized. (45 CFR §46.103(a) and (b)(5))

(Also see Decision Tree for Determining Whether an Adverse Event is an Unanticipated Problem: http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm#Q3)

WMREF IRB defines "unanticipated problem involving risks to participants or others" as an event that was (1) unforeseen, (2) related to the research procedures, and (3) caused either harm to participants or others, or placed them at increased risk of harm.

Investigators are informed of this requirement each time they receive an approval for a new study.

A. OCCURRING AT AN INTERNAL SITE: When the serious adverse event/unanticipated problem meeting the definitions and criteria above occurs at a local site (internal), the investigator needs to complete a WMREF Institutional Review Board Adverse Event Report Form (found on the website). This form records the investigator's assessment of the event according to the regulatory criteria above. It also asks for conclusions as to whether the event is already in the informed consent, and, if not, whether it should be added. All serious and unexpected events occurring at internal (local) sites will be reviewed by the full board.

Internal reports of death must be made to the IRB within 24 hours or the first business day after the event. Other Internal reports must be made within one week after the investigator's learning of the event.

All adverse events related to investigational devices will be reported to the full board regardless of the site, in compliance with 21 CFR 812.150(a)(1) and (b)(1).

Device reports of death at the local study site (internal) must be made to the IRB within 24 hours or the first business day after the event. Reports of other internal device events must be made within one week. External device reports must be made to the IRB within one week from when investigators first learn of the event.

B. OCCURRING AT AN EXTERNAL SITE :

1. Investigators must promptly report the following for adverse events occurring at an external site:
    a. All interim reports or status reports from a Data and Safety Monitoring Board, Data Monitoring Committee or other central monitoring entity *which contains new information about the study which may change the status of the study.*

b. Summaries of study-wide adverse events *which contains new information about the study which may change the status of the study.*

In cases where the IRB Office determines the external site report must be reviewed during a convened meeting of the IRB, the report is placed on the agenda for review. Additional information may be requested from the investigator. Reasons for placing the report(s) on the agenda for full review could include increased risks to subjects with potential changes needed in the informed consent or reconsenting, notification of subjects of new information, and such. Review of these events will be recorded in the minutes. Any need for additional information will be communicated to the investigator within five working days after the meeting.

External reports must be submitted in 2 weeks from when investigators first learn of the event. If the event is both serious and unanticipated, the report must be submitted to the IRB in one week.

C. POSSIBLE IRB ACTIONS:

The IRB may vote to take any of the following actions:

1.) Decide the report does not meet the criteria for a reportable unanticipated problem involving risks to subjects or others.

a. Accept the actions taken by the Principal Investigator to report and resolve the incident;
b. Ask for a clarification of data, more information, and/or follow up on the report;
c. Have the principal investigator notify participants when, in the judgment of the IRB, information about the unanticipated problem requires participants to be updated by information sheet, call and documentation, or reconsenting process;
d. Require modification of inclusion or exclusion criteria to mitigate the newly identified risks;
e. Require implementation of additional procedures for monitoring subjects;
f. Suspension of research procedures in currently enrolled subjects;
g. Require modification of informed consent documents to include a description of newly recognized risks; and/or
h. Other actions as deemed appropriate by the IRB.

D. REPORTING TO OTHER INSTITUTIONAL OFFICIALS: Unexpected, unanticipated problems involving risks to subjects or others that must be reported promptly (usually within one month of the IRB's receipt of the report, although more serious problems should be reported sooner) to institutional officials and any supporting department or agency head include:

1. Problems with data collection, data storage, privacy, or confidentiality;
2. Deaths;
3. Changes in approved research initiated without IRB review and approval to eliminate apparent immediate hazards to the participant;
4. Serious or continuing noncompliance with federal regulations or the requirements or determinations of the IRB;
5. Suspension or termination of research by the IRB;
6. Other problems the IRB believes need to be reported to the institution and/or regulatory officials.

E. INCIDENT REPORTING TO OHRP

Information included in an incident report to OHRP are:

1. Name of the institution conducting the research;
2. Title of the research project and/or grant proposal in which the problem occurred;
3. Name of the principal investigator on the protocol;
4. Number of the research project assigned by the IRB and the number of any applicable federal award(s);
5. A detailed description of the
   a. Problem
   b.Noncompliance
   c. Reason for the suspension or termination; and
   d.The action the institution is taking or plans to take to address the problem, noncompliance, or suspension or termination.

(From OHRP Guidance on Reporting Incidents, 052705)
http://www.hhs.gov/ohrp/policy/ inc idreport_ohrp.ht ml

(OHRP Guidance of Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others, January 15, 2007)
Guidance can be found on OHRP Website at:
http://www.hhs .gov/ohrp/policy/AdvEvntGuid.htm
(Active on 040508)

IX. MONITORING OF RESEARCH

A. Continuing Review

All ongoing research will, unless meeting the criteria for expedited review, undergo full board review before the date of final approval. In conducting the continuing review, the IRB will review, at a minimum, the protocol and any amendments as well as a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from research, or complaints about the research; (c) a summary of any recent literature, findings, or other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document.

A primary reviewer will be assigned by the IRB Chair or IRB Office for each study to be reviewed. The primary reviewer will have a copy of the complete protocol including any modifications previously approved by the IRB, as well as all of the rest of the above information. All other IRB members will have a summary of the protocol instead of the complete protocol. The complete protocol will be available at the IRB meeting. All other IRB members will also receive the report detailing items (a) through (d) above.

Review of the currently approved consent document must ensure that the information is still accurate and complete. Any significant new findings that may relate to the subject's willingness to continue participation should be provided to the subject in accordance with 45 CFR §46.116(b)(5). Review of currently approved or proposed consent documents must occur during the scheduled continuing review of research by the IRB, but may be done more frequently if new information becomes available.

Projects which need verification from sources other than the investigator that no material changes have occurred since the previous IRB review are those projects for which the Principal Investigator or physician overseer is no longer credentialed by the Medical Staff Office and projects conducted by investigators who previously have failed to comply with the requirements of the Federal regulations or the requirements or determinations of the IRB. (21 CFR §56.108(a)(2)) The other condition for projects requiring outside verification will be when the results of the IRB monitoring of a project reveal changes or occurrences that have not been reported previously to the IRB. Once a PI or project is identified as requiring outside verification, monitoring will continue on a routine basis with a time line recommended by the IRB for that case. (See also "VIII. D. Documentation of Investigator Delinquency/Deficiency.)

B. IRB Monitoring of Ongoing Research

Throughout the year, the WMREF staff will conduct, with the help of IRB members, monitoring of the research process. The monitoring will be conducted on a random basis or on a for-cause basis. The "IRB Regulatory Monitoring Checklist" will first be filled out in the IRB Office with dates of latest Protocol, Amendments, Consent, Adverse Reaction reports, etc., found in the study's folder. This checklist will be taken to the research site for comparison purposes. The entire checklist will be filled in, and if applicable, a copy of the latest monitor's comment sheet will be attached.

Any discrepancies found will be worked through with the study staff, PI, and IRB Office. Significant problems will promptly (within two days) be reported to the IRB Chair. The IRB Chair will decide if any immediate additional actions need to be taken, as well as whether the matter is to be brought before the full board.

The random monitoring will be conducted as IRB scheduling and personnel allow, with no specific number required each year. The for-cause monitoring will be done based on the following findings:

1. Continuing review materials include items that were not previously reviewed or approved by the IRB;
2. The IRB Office receives notification from investigator that they are missing IRB/regulatory materials;
3. There is a pattern of incorrect submission materials; or
4. Significant and/or continuing non-compliance with the federal, state, and/or local regulations or the requirements of the IRB by the investigator. This situation also requires prompt reporting (within seven days) to the appropriate institution and to the FDA and/or OHRP.

(21 CFR§56.108(b)(2))

C. Oversight of Informed Consent Process

Throughout the year, the WMREF staff will conduct, with the help of IRB members, random reviews of the informed consent process, with no specific number of reviews required each year. The IRB staff has developed and will continue to enhance a checklist to be used for this oversight. In addition, the monitors will be asked to write a paragraph describing the process that they observed and any questions, comments, or criticisms. The completed checklist and summary account will be brought to the IRB Director. If significant problems are found, they will be reported promptly (within two days) to the IRB Chair. The IRB Chair will decide if any immediate additional actions need to be taken, as well as whether the matter is to be brought before the full board.

Each month studies due for continuing review will be randomly chosen to provide the IRB Office with copies of all signed consents from the study to date. These will be checked for completeness and accuracy.

D. Documentation of Investigator Delinquency/Deficiency

A file will be kept in the IRB Office of investigators for whom there has been a problem with delinquency of reports, deficiencies found upon monitoring, studies closed due to investigator noncompliance, and such. This will include any request by the IRB that a note be placed in the investigator's file. Files will be maintained in alphabetical order by investigator last name, then chronologically with newest entries on the top of the file. These will be used to make monitoring choices, decisions of length of review, and when new studies from pertinent investigators come to the IRB for review.

X. IRB MEETING PACKETS FOR MEMBERS

For IRB meetings, material for review by members will be available at least one week before the meeting date. The packet of materials will include all of the following as applicable for the upcoming meeting:

a. Agenda
b. Minutes of the last meeting
c. Educational material, including an update on regulatory information
d. Old Business
    1. Revisions from previously presented studies
    2. Emergency use requests to the Chair since the previous meeting
    3. Research being presented with changes
    4. Modification Log
    5. Other old business
e. New Research Proposals
    1. WMREF IRB Application (Investigator summary of protocol)
    2. Protocol (Primary reviewer may have only copy of full protocol for certain studies e.g. cancer group protocols, but full protocol will be available at the meeting. In such cases, other members will have investigator summary of protocol.)
    3. Investigator's brochure (usually to the primary reviewer only, and available in full at the meeting)
    4. Consent form(s)/permission/assent/authorization or request for waiver of informed consent or request for waiver of documentation of informed consent
    5. Authorization, if separate from the consent; or request for waiver of authorization; or limited data set materials; or de-identification certification form as required by the HIPAA Privacy Rule.
    6. Patient materials such as diaries or logs
    7. Advertising material
    8. Study specific standing orders for research occurring within the hospital
f. Amendments to Protocol
    1. Sponsor's letter regarding same
    2. Investigator's cover regarding same
    3. Copy of protocol change(s)
    4. Copy of protocol (when changes are numerous) with date of revision
g. Amendments to Consent Form
    1. Sponsor's letter regarding same
    2. Investigator's letter regarding same
    3. Consent form currently in use (May go to primary reviewer and be available at meeting)
    4. Newly amended consent form with date of revision
h. Severe Adverse Events (Internal and External) and/or Safety Reports
    1. Sponsor's letter regarding same
    2. Investigator's letter regarding same
    3. MedWatch Form
    4. Completed Severe Adverse Event reporting form including assessment of causality by investigator and recommended consent changes, when needed
i. Data Monitoring Committee Reports

j. Continuing Review
    1. Completed continuing review form
    2. Copy of currently approved consent form
    3. Protocol (Primary reviewer may have full copy, other members will have protocol summary. Full protocol available at meeting.)
    4. Research progress report (from IRB Office Database, when available)

k. Miscellaneous (Additional items as warranted)

Some materials will be sent to members by e-mail. These items include minutes of the prior meeting, items qualifying for exemption, expedited review, facilitated review, final reports, and a list of qualifying unanticipated problems/serious adverse events. The IRB agreed this would save paper and printing as well as staff time. All materials are available in full at the IRB meetings.

Continuing education items and other articles of interest will also be sent to IRB members by e-mail when events or materials that concern ethical research are available and/or will not all fit in the IRB Continuing Education portion of the agenda due to time constraints.

XI. TRAINING OF IRB MEMBERS

A. Orientation of New Members

New members will go through an orientation process. Each new member will sit in on two IRB meetings as visitors (non-voting) as the first step of orientation. This will be followed by a one-on-one orientation with the IRB Director to go over procedures and answer questions. New members are also required to complete a designated computer based training program in Human Subjects Protections and HIPAA for Research. After this has been completed, the member will have full voting privileges. Members are informed of website links containing the WMREF IRB Policies and Procedures and pertinent ethical guidances and resources to use while they serve on the IRB. (FIS VIII., E.)

B. Continuing education will be provided for IRB members by the staff of the IRB Office and occasional guests on a monthly basis. The educational session will usually take place at the beginning of each IRB meeting. Education will include the history of the IRB process, the applicable parts of the Code of Federal Regulations, IRB policies and procedures, and new developments pertaining to the IRB. Newsletters are made available to members on a monthly basis on the state of affairs nationally.

C. Reference Materials

The IRB Office will serve as a resource for reference materials. The WMREF IRB staff are available to assist IRB members and investigators anytime the Office is open. The reference material resources might include a series of youtube videos from NIH, pertinent Code of Federal Regulations, materials from national IRB conferences, copies of materials used for previous continuing education sessions, books and booklets on the protection of human subjects, as well as material on clinical study design and clinical ethics. Some of these references are cited below:

- 21 Code of Federal Regulation (CFR) §50,54,56,312,812
- 45 CFR §46
- The Belmont Report
- The Nuremberg Code
- The Declaration of Helsinki
- Protecting Human Research Subjects, OHRP IRB Guidebook
- DHHS, FDA Information Sheets
- Amdur, R.J. and Bankert, E.A. INSTITUTIONAL REVIEW BOARD: Management and Function 2nd edition. Boston: Jones and Bartlett Publishers, 2006.
- Amdur, RJ and Bankert, EA.. INSTITIONAL REVIEW BOARD (IRB) Member Handbook. Boston: Jones and Bartlett Publishers, 2011.

XII. IRB TIMELINE FOR NEW RESEARCH APPLICATIONS

A. The IRB deadline for new research proposals is the first business day of each month. Communication between the IRB Office and Investigators commonly takes place between the deadline for study submission and the date of the IRB meeting. When resolution of issues such as changes or additions to the submission are not completed by 9:00 AM on the Monday morning 10 days (usually 7 working days) prior to the IRB meeting, the research study concerned will be moved to the next month's agenda. The WMREF IRB Office will notify the Principal Investigator and/or the Research Coordinator whenever this is the case. This requirement allows for sorting, copying, collating, and timely delivery of packets to IRB Members by the IRB Staff.

B. During the first 30 days following any proposal submission to WMREF's IRB, an IRB primary reviewer will review the study and will work with the principal investigator to make initial modifications if necessary. This usually involves modifications to the informed consent. This process may be facilitated when the principal investigator uses the approved WMREF IRB Consent Form Checklist in formulating the consent.

C. After primary review as noted in B above, research proposals will be presented at the next regularly scheduled IRB meeting. At this time, the IRB full board may require further modification. Investigators who do not submit required modifications within 90 days of the date of the IRB letter listing modifications will have their studies administratively terminated. There is no reactivation. Studies must be resubmitted in full if they were administratively terminated.

D. Investigators should be aware their proposals will usually require 60 days for final approval. However, proposals requiring little or no modification may receive IRB approval in 30 days, and some may take longer than 60 days.

XIII. NON-MEMBER INVESTIGATOR ATTENDANCE AT IRB MEETINGS

A. The IRB requires the principal investigator or co-investigator and/or an appropriate representative capable of answering questions of study design, safety, and human subject protection plans to be present during the review of each new study. If no investigator is present for the meeting, the research proposal will be tabled until the next meeting. The IRB may waive this requirement on a case-by-case basis when the Board has no questions for the investigator. Should the investigator know ahead of time that he/she will be unable to attend, the WMREF IRB Office should be notified.

B. Principal investigators are asked to meet outside the meeting room.

C. An IRB staff member will call the investigator into the meeting room when it is time to present his/her study.

D. The principal investigator is asked to give the Board a brief overview of the study. The Board will then ask any questions they may have.

E. After this, the investigator is asked to leave the meeting room so the Board can complete their discussion and voting.

F. Investigators who are not members of the WMREF IRB will not receive a copy of the agenda. Instead, a reminder will be sent regarding the time and location of the meeting, the title of the study to be reviewed, and an approximate time for the pertinent investigator's presentation.

XIV. OTHER NON-MEMBER ATTENDANCE AT IRB MEETINGS

A. Requests to observe the IRB process may be submitted to the Chair or Vice-Chair or the IRB Office for consideration. Approvals by the Chair or a Vice-Chair will include notification of the IRB Office.

B. Individuals who do sit-in to observe must maintain complete confidentiality regarding the specifics of the research reviewed and remarks made through the course of the meeting.

They must sign the WMREF IRB Confidentiality Agreement before the meeting starts.

XV. RECORDS AND DOCUMENTS

A. The IRB Office will keep an up-to-date record listing all members and alternates of the IRB and their qualifications.

B. The policies and procedures of the IRB will be kept in the IRB Office, and will be reviewed at least every three years. Changes in the policies and procedures will be proposed by the IRB Director and/or IRB members and reviewed by the IRB Chair and WMREF Executive Director before being sent to the WMREF Board of Directors for final approval.

C. The IRB Office will keep all records of protocols, informed consents, HIPAA authorizations, waiver requests, adverse reaction reports, amendments, continuing reviews, correspondence, statements of significant findings provided to subjects, etc., in a single file for each study and investigator or investigator group. If the same study is approved for different principal investigators, each will have its own corresponding file. Emergency use reports will be kept on file for a minimum of three years, as will budget and accounting records pertaining to any particular study.

D. Records as noted above will be kept for a period of at least three years from the close of a research study or from the date of last activity of a study, whichever occurs later. Records (including minutes of IRB meetings) will be kept for a minimum of at least three years even for research which is never conducted, e.g., either studies never approved, or those studies that do not end up enrolling a single participant before closing, in order to comply with federal guidelines.

E. The IRB Office will also maintain Institutional Review Board minutes and transmittals on actions, instructions, or conditions of approval. The records noted in this section (including study records) are continually reviewed by the administrative staff for informational content and follow-up concerning additional information requested, conditions of approval, etc.

F. The records of the IRB pertaining to individual research activities supported by federal funds and/or covered under a Federal Wide Assurance are subject to inspection by the Department of Health and Human Services Office for Human Research Protection (OHRP) and/or the Food and Drug Administration (FDA). Except as otherwise required by law, information that can be identified with a particular subject of research or related activity will not be disclosed except:

1. With the consent of the subject or legally authorized representative; or
2. As may be required by the Department of Health and Human Services or the Food and Drug Administration.

XVI. IRB REGISTRATION

The IRB will maintain registration as required by OHRP and the FDA. Required registration must be updated every three years, or more frequently when certain changes, as documented in the guidance occur. It is the responsibility of the IRB Office and, specifically, of the IRB Director, to see that registration remains current.

Information required includes contact information for the IRB and various people associated with the IRB, an approximate number of active protocols of FDA-related research, and a description of the type of FDA- products the IRB reviews (such as biologicals, drugs, and devices.)

(See FDA Guidance – Frequently Asked Questions – IRB Registration, July 2009)
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/default.htm

XVII. STAFFING AND RESOURCES

A. WMREF will provide all necessary clerical and administrative support to conduct IRB meetings at least monthly. Such support will include, but not be limited to the following:

1. Preparation of agenda, which includes gathering and clarifying all new study proposals to be presented. This will include all editing, copying and dissemination of current month agenda items to all current IRB members.
2. Provide all support for the monthly IRB meetings, which may include the following: Setting meeting times and locations, preparation of room, including food service, necessary administrative personnel support, including secretarial support.
3. IRB post-monthly meeting support includes preparation of monthly meeting minutes, letters to investigators/sponsors concerning status of research proposals, and follow-up phone calls for clarification of any matters needing resolution.
4. Provide administrative support for documentation, correspondence and maintenance of records as required.

B. WMREF provides professional ongoing support to provide educational opportunities for all IRB members and investigators. Such educational opportunities will be provided during monthly IRB meetings and on an ongoing basis.

C. WMREF provides professional support in the IRB's continuing review of approved active study proposals. This support will include review of all adverse events, annual and final reports and amendments, such as changes in investigators, sites, changes in protocol, etc.

D. WMREF provides office space as well as supplies, computers, copying equipment, and filing space for the IRB.

E. Wesley Medical Center provides WMREF with adequate funding to provide the above necessary support for the research activities conducted at Wesley Medical Center or its affiliated facilities. Wesley Medical Center may provide an adequate meeting facility for the monthly IRB meeting and access to catering support to be paid for by WMREF.

F. Liability coverage for IRB members and alternates is provided by WMREF, regardless of the member's/alternate's employment status.
(FIS Appendix H, VII, G, H)

XVIII. INVESTIGATOR RESPONSIBILITIES

A. Requirements for New Projects (See also Section C of Appendix for Research Application and WMREF Research Guide**) as applicable**

1. Study specific standing orders, or a statement that the study does not involve physician orders.
2. Study Protocol (21 CFR §56.115(a)(1))
3. Investigator's Summary
4. Curriculum Vitae of each Investigator (FIS Appendix H, XI, A.)
5. Proof of Human Subjects Protection Training or Training Renewal for The Principal Investigator and other key study personnel
6. Informed Consent Document (21 CFR §56.111(a)(4-5) and §56.111(a)(1)) or request for waiver
7. IRB Consent Form Checklist
8. HIPAA Authorization for Use and Disclosure in Research (or incorporated in the informed consent document) or request for waiver or HIPAA De-Identification Form (45 CFR §164.506 and 46.512(i)(i))
9. Completed FDA Form 1572 and Copy of Investigator Drug Brochure (for investigational drugs) or Copy of Investigator Device Brochure (for investigational devices) (21 CFR §56.111(a)(2), §56.115(a)(1) and 21 CFR §312.55)
10. A list of all tests, medications and procedures that would not routinely be obtained in a non-research setting, and an indication of who will be billed for these.
11. Report Potential Financial Conflict of Interest(s)

B. Investigators' Responsibilities:

1. Ensuring that all research proposals involving human subjects are submitted to and approved by the IRB prior to initiation of the research. Research investigators submitting a protocol will not make the final determination of exemption from applicable Federal regulations or provisions. If the investigator has reason to believe the protocol is exempt from IRB review and approval, he/she will fill out a WMREF IRB Exemption Certification Application and cite the number of the exemption. The Chair of the IRB, or his/her designee, will then make the final decision on exemption status. If the Chair or his/her designee determines the protocol to be exempt from review and approval, nothing further is required.

2. Complying with all IRB policies, decisions, conditions, and requirements. Investigators are responsible for ensuring that the research is implemented as specified in the approved IRB protocol.

3. Human Subject Training and Renewal per Federal Register Volume 73, Number 127 (Tuesday, July 1, 2008)] [Notices] [Pages 37460-37463]

   a. The Principal Investigator and other key study personnel (defined below in XVII.B.3.c. and XVII.B.3.d. but more generally all persons who will have a significant role in the design or conduct of research) must complete human subjects protection and HIPAA research training prior to receiving study approval through the WMREF IRB. The KUSM-W

computer-based training program is recommended, although others may be acceptable. Individuals should check with the IRB office regarding other training to assure their training meets the WMREF requirements. A copy of the certificate verifying completion of training must be turned in for each investigator and other key study personnel before study approval can be received from the WMREF IRB. Alternately, the WMREF IRB will accept direct confirmation from the KUSM-W Research Compliance Officer as verification of human subjects protection and HIPAA original and renewal research training.

b. Renewal training for the Principal Investigator and other key study personnel (defined below in XVII.B.3.c. and XVII.B.3.d. but more generally all persons who will have a significant role in the design or conduct of research) will be dictated by research base guidelines. For studies that do not have research base guidelines, renewal of human subjects protection and HIPAA research training will be required every three years, calculated from the date of last completion.

Human Subject Training Renewal will be monitored at the time of continuing review. If Human Subject Training will or has lapsed by the study's annual review expiration date the Human Subject Training Renewal must be completed prior to the study's annual review expiration date and to receive continuing review approval.

c. The following constitute key study personnel:

- Principal Investigator
- Sub-Investigator(s)
- Research coordinator(s), project manager(s)
- Any individual(s) responsible for obtaining informed consent to participate in research
- Any individual(s) who are individually named on a grant or contract application
- Any individual(s) listed on an FDA form 1572
- Any individual(s) who are named as a contact person in the informed consent document
- Any individual(s) named on recruitment materials for research
- Any individual(s) who provide supervision of the persons who are obtaining informed consent to participate in research
- Any individual(s), including student researchers and coordinators, who are involved with the research by handling protected health information or are using the research information/data set as part of their own research

d. If students or other individuals have minor roles in the research that are not listed above, they are not required to be listed on the research protocol. Hospital employees who are performing procedures required by the research which are standard of care, required during their normal course of work, are not considered key research personnel. However, the Principal Investigator is responsible to ensure that these individuals receive both adequate training, including human subjects protection

training and oversight in accordance to the roles these individuals perform in the research.

4. Obtaining and documenting informed consent and providing a copy of the IRB approved consent form to each subject, unless the IRB has specifically waived this requirement.
5. Ensuring that assent from research participants who are minors (under 18 years of age) is obtained and documented in accord with the IRB policies and requirements.
6. Obtaining and documenting HIPAA authorization for use or disclosure of protected health information in research, unless the IRB (acting as Privacy Board) has specifically waived this requirement. In the event of a waiver of authorization, the investigator is responsible for ensuring documentation of use and disclosure of protected health information is completed in accordance with the requirements of the institution where the research is taking place and with the HIPAA Privacy Rule. (45 CFR §164.528)
7. Reporting progress of approved research to the IRB, as often as and in a manner prescribed by the IRB on the basis of risks to participants, but no longer than once per year, (21 CFR §56.108(a)(1) and §56.115(a)(1,3 and 4)) and, at the end of the study, furnishing the IRB with a final report.
8. Promptly submitting to the IRB any modifications to a protocol or consent form of an approved protocol when:
   a. it is proposed to involve human participants, and the activity previously approved has only indefinite plans for the involvement of human participants, or
   b. it is proposed to change the previously approved human subject research activities. The changes cannot be initiated without IRB review and approval except where necessary to eliminate any immediate risks or hazards to the participants. This would include any modifications to the IRB approved consent form. Investigators shall forward to the WMREF IRB Office a memo requesting approval for the modification, indicating what changes are required and attach a copy of the protocol document (including any modified consent and HIPAA forms). (21 CFR §56.108(a)(4) and §56.115(a)(3-4))
9. Promptly report any injuries, adverse events or other unanticipated problems involving risks to participants and others to the IRB and then to the sponsor, the institution and any applicable Federal, state, and/or local department. (21 CFR §56.108(b)(1), §56.115(a)(3-4), §56.115(b)(1) and §56.113))
10. Acknowledging and accepting their responsibility in protecting the rights and welfare of human research participants and for all applicable provisions of the WMREF policies dealing with the protection of human participants.
11. When applying for IRB approval, the investigator will provide to the IRB:
    a. Professional qualification to do the research (including a description of necessary support services and facilities)
    b. Investigator's Summary Sheet (See template in Appendix.)
    c. Study protocol which includes and/or addresses (21 CFR §56.103(a) and §56.115(a)(1)), as applicable:
        i. Title of the study
        ii. Purpose of the study (including the expected benefits obtained by doing the study)
        iii.. Sponsor of the study (if any)

iv. Results of previous related research
v. Subject inclusion/exclusion criteria
vi. Justification for the use of any special/vulnerable subject populations (for example, the decisionally impaired, children)
vii. Study design (including as needed, a discussion of the appropriateness of research methods)
viii. Description of procedures to be performed
ix. Provisions for managing adverse reactions
x. The circumstances surrounding consent procedure, including setting, subject autonomy concerns, language difficulties, vulnerable populations
xi. The procedures for documentation of informed consent, including any procedures for obtaining assent from minors, using witnesses, translators and document storage
xii. Compensation to subjects for their participation
xiii. Any compensation for injured research subjects
xiv. Provisions for protection of subject's privacy
xv. Extra costs to subjects for their participation
xvi. Extra costs to third party payers because of subject's participation

d. Investigator's Brochure (when one exists) [3 copies] (21 CFR §56.111(a)(2), §56.115(a)(1), and 21 CFR §312.55)
e. Case Report Form (when one exists)
f. The proposed informed consent document (21 CFR §56.111(a)(1,4-5) or Request for Waiver
Containing all the requirements of 21 CFR 50.25(a)
1. Containing requirements of 21 CFR §50.25(b) that are appropriate to the study
2. Meeting all requirements of 21 CFR §50.20
3. Translated consent documents, as necessary, considering projected subject population(s)

g. HIPAA Authorization Form or Request for Waiver or De-Identification Form
1. Translated HIPAA authorization forms, as necessary, considering likely subject population(s)

h. WMREF IRB Financial Conflict of Interest Report Form

12. The Wichita Medical Research and Education Foundation (WMREF) Institutional Review Board (IRB) is charged with reviewing potential cases of financial conflict of interest regarding research personnel and study staff that may affect or appear to affect research. Before a proposed study is approved, the Principal Investigator must file a current WMREF IRB Financial Conflict of Interest Report Form for each proposed study.

a. When potential conflict(s) of interest is/are identified or reported the WMREF Office will determine how best to manage reported conflict(s).

b. The WMREF Office will evaluate reported interests to judge whether they might adversely affect the protection of participants.

c. In general, the WMREF Office will consider anything above $5,000 in individual stock holdings or 5% in single entity holdings as the threshold for a potential conflict of interest however the WMREF Office will recognize and honor any policy that is more restrictive.

d. If it is determined there may be an adverse effect, the WMREF Office will work collaboratively with the investigator and institutional officials to manage the conflict(s) on a case-by-case basis, considering the risk level of the research, to include the possible addition of appropriate disclosure(s) to the participant in the consent form disclosed in a separate section titled "Investigator Compensation" prior to WMREF IRB approval.

e. If the WMREF Office is unable to negotiate a solution it will be taken to the WMREF IRB for resolution.

To the extent permitted by law, all Statements, letters, other records and information submitted will be maintained confidentially by the IRB Office and IRB members. Statements, other records and information, however, will be made available to any federal agency funding research upon written request of the agency, and otherwise as required by law.

C. Maintenance of Study Files

The investigator will maintain a protocol file with all correspondence between the investigator and the IRB as well as communications regarding the study from a sponsor. He/she will also maintain copies of the signed consent forms and HIPAA Authorization forms, any data derived from the study, progress reports, and reports of all unanticipated problems/adverse incidents and any follow-up to them. Length of maintenance will be as specified in the federal regulations.

D. Registration of Clinical Trials

Registration of clinical trials is a free service of the U.S. National Institutes of Health (developed by the National Library of Medicine). The website is www.ClinicalTrials.gov . ClinicalTrials.gov is a directory of federally and privately supported research trials conducted anywhere in the world to test the effect of experimental drugs, devices, and procedures for many diseases and conditions.

This registration has been available for a number of years, but was not made mandatory for applicable trials until 2009. Clinical trials of human subjects that are prospective in design qualify for registration. Registration is mandatory for investigational new drug (IND) efficacy trials for serious diseases and conditions by law: Section 113 of the FDA Modernization Act. The International Committee of Medical Journal Editors (ICMJE) requires trial registration as a condition for publication of research results generated by a clinical trial. It is preferable that the trial be registered prior to the enrollment of the first participant.

Registration can help with enrollment to trials, encourages the sharing of new information, and is intended also to help researchers eliminate trial duplication, including duplication where the outcome of the research is negative.

The website is very user friendly, and registration information includes a summary of the trial protocol, including the purpose, recruitment status, and criteria for patient participation. Trial locations and specific contact information are provided to assist enrollment.

While many study sponsors will register a multi-site trial, it is the responsibility of the principal investigator to see that the study is registered. The IRB, as part of its educational efforts with investigators, provides information and materials on the registration of applicable clinical trials when such a trial is first approved by the IRB. The IRB requires the investigator to report the ClinicalTrials.gov Identifier (three alpha characters followed by eight numeric characters) within 30 days of IRB approval. These are logged by the IRB for reference.

XIX. SUBJECT RECRUITMENT

A. Subject Population

Choice and recruitment of a study population is to be conducted under the terms of Justice, as espoused in the Belmont Report, a copy of which can be obtained from the IRB Office.

B. Advertising

FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process. Advertisements and any other type of solicitation for potential human research subjects should be submitted to the IRB for review and approval by the IRB as part of the package for initial review. If, however, the clinical investigator decides at a later date to advertise for subjects, the advertising may be considered an amendment to an ongoing study. When advertisements are easily compared to the approved consent document, the IRB Chair, or other designated IRB member, may review and approve by expedited means, as provided in 21 CFR §56.110(b)(2). When the reviewer has doubts or other complicating issues are involved, the advertising should be reviewed at a convened meeting of the IRB.

The WMREF IRB shall review the text message of each advertisement, and consider its impact in light of the distribution medium, to ensure that the following are all fairly and accurately represented: (a) the nature of the study, (b) the identity of the investigator, (c) the importance of the knowledge that may reasonably be expected to result, and (d) potential risks and benefits. In addition, the IRB must consider whether the submitted advertising plan is consistent with the principle of "equitable selection of subjects."

The Principal Investigator is required to obtain permission for every advertising initiative (bulletin board, newspaper, radio, television, web site, etc.). If the IRB has previously approved the message text of an advertisement for one medium (e.g., newspaper), the investigator may not distribute the same message via a different medium (e.g., web site) without the approval of the IRB.

1. **1-800 Recruitment**

   The following are general guidelines to follow when a sponsor advertises for people who are interested in a particular study to call a toll-free number.

   a. If there is an ad and the WMREF IRB has not yet or does not approve it, then the ad may run but the recruiters may not refer contacts to our investigator(s), institution, or study site(s).

   b. The IRB will review the phone scripts used by the sponsor in response to the call from the potential subject to the 1-800 number.

   c. In evaluating the phone script, no one should be asked for identifying information before the interview is complete.

   d. The telephone script should include a quick basic introduction: who "we" are, what "we" are doing, why, do you have the time to help now and, if not, when can "we" reschedule.

   e. At the end of the interview, the interviewer should say thank you, and then indicate if the person is eligible. If the person is eligible and

would like to participate, could the interviewer please have (identifiers, such as name, address, age, sex, race)? Requests for identifying information should only come at the end.

f. If the person did not qualify but the sponsor wants his or her name for a database to contact in the future or for some other reason, this should be explained very clearly. People contacted have the right (Respect for Persons – Belmont Report) to decline to be included in any such database.

2. **Direct Phone Calling (Telemarketing)**

Because there is a subset of people for whom an unwanted telephone call or home visit constitutes a greater than minimal risk, the normal procedure should be to solicit consent for the intrusive contact (for example, a letter with a return postcard).

The IRB understands that this may introduce a selection bias into some studies. In some cases, that is simply a 'cost' of doing the research in an ethical manner (that is, it is a different bias, but not necessarily a worse bias, than that introduced by those who refuse because they reject a cold call).

The IRB recognizes that there may be studies in which such a bias is particularly problematic, and in which the only subjects at risk are those included purely by chance in an unselected population. Some such studies may even provide offsetting benefits to participants. In those cases, it MAY be acceptable to make the contact without prior consent.

From a regulatory perspective, there MAY be circumstances that would allow an IRB to make a finding of no-more-than-minimal-risk and thus to waive the requirement for prospective consent. Such as:

a. The intent to contact must be announced (e.g. by letter) in advance;
b. The announcement must be so presented that it is unlikely to be overlooked as "junk mail;"
c. The announcement must PROMINENTLY provide a GENUINELY ACCESSIBLE means to register dissent (e.g. 24-hour voice mail), with an adequate time interval to do so;
d. The people telephoning must be adequately trained to begin with a very clear statement of voluntarity, a meaningful assessment of the ability of that person to give consent, and a solicitation of genuine consent before proceeding with the survey;
e. Telemarketers' conversion techniques may not be used (“no” means “no");
f. "No solicitors" pre-recording must be honored as "No research surveys, either;"
g. Professional telemarketers may not be used unless the necessary special training and monitoring can be provided;
h. "Per COMPLETED response" payments may not be used;
i. It is the investigator's responsibility to (a) ask for this special provision, (b) document that the provision is necessary, and (c) document that all the provisions have been met.

Whoever "obtains consent" should co-sign the consent form and the subject should be given a copy of the consent document or script. This is real time co-signing instead of the Principal Investigator signing and dating later. This shows that there are two parties -- the giver and the receiver of information -- and both parties are taking responsibility by putting their names on the line.

XX. GLOSSARY

AIDS	Acquired Immune Deficiency
Assent	A child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. (45 CFR §46.402(b))
CDC	Center for Disease Control and Prevention
CFR	Code of Federal Regulations
CRF	Case Report Form
Children	Persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.
Consent	The affirmative agreement by a competent adult to participate in treatment or procedures involved in research.
FDA	Food and Drug Administration
FIS	Food and Drug Administration Information Sheets
FR	Federal Register
HDE	Humanitarian Device Exemption
HHS	(Department of) Health and Human Services
HSC	Human Subjects Committee (another name used for IRB)
HUD	Humanitarian Use Device
IDE	Investigational Device Exemption
Identifiers	Names, unique numbers, or codes that could conceivably be traced back to names. The term also applies to unique identifying characteristics that might reasonably contribute to the discovery of the subject's name.
IND	Investigational New Drug
IRB	Institutional Review Board
MS	Multiple Sclerosis
NIH	National Institutes of Health
OHRP	Office for Human Research Protection
Permission	Agreement on the part of the parent(s) or legally authorized representative of a child for that child to participate in a research study (often spoken of as consent, although the federal term is permission)
PI	Principal Investigator
WMC	Wesley Medical Center
WMREF	Wichita Medical Research and Education Foundation