INSTITUTIONAL REVIEW BOARD

Policy and Procedure Manual

Approved by:

Matthew Johnson, MD, MBA, IRB Chairperson

E.W. Tibbs, President & CEO
Centra Health

Origin Date: Version 1 January 1990
Update: Version 2 October 4, 1990
Reviewed: Version 3 January 2000
Recommendations IRB P&P Committee: 9/25/09, 12/9/09; Approved by Full Board: V. 4 1/13/2010
Recommendations IRB P&P Committee 2/16/11 and 2/21/11; Approved by Full Board: V. 5 2/22/2011
Recommendations IRB P&P Committee 5/25/11; Approved by Full Board: V. 6 June 22, 2011
Recommendation IRB P&P Committee: November 2, 201; Approved by Full Board: V. 7 January 11, 2012
Approved by Full Board: Version 7a December 18, 2012 (no changes)
Recommendation IRB P&P Committee: 10/15/12, 11/02/12, 11/07/12, 1/10/13; Exec Committee 11/27/12, 12/17/12; Approved by Full Board: Version 8 January 15, 2013
Recommendation IRB P&P Committee: 5/2/13; Approved by Full Board: Version 9 June 18, 2013
Recommendations Ad Hoc committee (6.25.13) and IRB P&P Committee (9.06 & 30.13); Approved by Full Board: Version 10 October 15, 2013
Recommendation P&P Committee 12MAR2014 approved by Full Board: Version 11 22APR2014
Recommendations made at the Full Board meeting approved by Full Board: Version 12 20MAY2014
Recommendations P&P Committee 9/3/14 approved by Full Board: Version 13 23SEP2014
Recommendations Policy Committee (1/30/15; 2/11/15) approved by Full Board: Version 14 25FEB2015
Recommendation Policy Committee (3/23/15) approved by Full Board; Version 14a 21APR2015
Recommendation Policy Committee (3/23/15) approved by Full Board; Version 14b 23JUN2015
P&P Committee meeting 1/6/16, 8/23/16; 9/8/16, 10/19/16, 11/9/16
Recommendation Policy Committee (11/9/16) approved by Full Board; Version 15 15NOV2016
Recommendation Policy Committee (12/19/17) approved by Full Board; Version 16 19DEC2017

Centra Health Institutional Review Board

STATEMENT OF COMPLIANCE
(USA)

Name of IRB: __Centra Health IRB_____

IRB Address: __1901 Tate Springs Road_____

__Lynchburg, VA 24501_____

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The Centra Health Institutional Review Board ("IRB") for Clinical Investigations is duly constituted, fulfilling all requirements for diversity, and has written procedures for initial and continuing review of human research protocols. The IRB complies with all U.S. regulatory requirements related to the protection of human research participants. Specifically, the IRB complies with 45 CFR 46, 21 CFR 50, 21 CFR 56, 45 CFR 160, 45 CFR 164, and the Guidelines of the International Conference on Harmonization as adopted by the U.S. Food and Drug Administration related to Good Clinical Practice.

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K. Code of Federal Regulations Title 21 – Food and Drugs, Part 56 – Institutional Review Boards, *21CFR 56.101-124*. Revised April 1, 2017. Also available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56&showFR=1

L. Code of Federal Regulations Title 45-- Public Welfare, Part 46 -- Protection of Human Subjects, *45 CFR 46.101-505*. January 15, 2009. Also available at http://www.hhs.gov/ohrp/policy/ohrpregulations.pdf.

M. Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies January 2006. Also available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf.

N. AAMC Principles for Protecting Integrity In the Conduct and Reporting of Clinical Trials – January 6, 2006 (Anthem)

CENTRA HEALTH, INCORPORATED
INSTITUTIONAL REVIEW BOARD

POLICIES AND PROCEDURES

I. CHARGE TO THE BOARD

The Institutional Review Board (IRB) shall be charged with safeguarding the rights and welfare of Centra patients who are/or may potentially become subjects of investigational activities. Further, the IRB is available to review other investigational activities involving human subjects that are initiated elsewhere in the medical community. It is the responsibility of the IRB to review, take action on, and monitor all proposed research activities conducted by the staff or other agents of Centra Health, Inc. based on current federal or other regulations regarding investigational activities in human subjects. Relevant federal regulations are attached in the Appendices[1] to this Manual. Further, the IRB also adopts the Institutional Review Board Guide Book OHRP IRB Guidebook prepared by the Federal Office for Protection from Research Risks as a resource to utilize in the conduct of its activities. This is located on the Centra IRB Member Education website. The IRB is responsible to the President/CEO of Centra Health, Inc. The IRB will keep minutes to the official IRB meetings available on the website https://centrahealth.sharepoint.com/sites/irb/default.aspx for the Board of Directors of Centra Health, Inc. and the Executive Committee of the Medical Staff at their request.

II. DEFINITIONS

"Office for Human Research Protections (OHRP)"—OHRP is a federal agency which provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS). OHRP is part of the Office of the Assistant Secretary for Health (OASH) in the Office of the Secretary (OS), U.S. Department of Health and Human Services.

"Principal Investigator"—The local clinical expert or scientist primarily responsible for leading a particular clinical study.

"Significant Risk" Device Study—Under 21 CFR 812.3(m)[2] an SR device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

[1] Appendix J – Also available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1;
Appendix K – Also available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56&showFR=1
Appendix L – Also available at http://www.hhs.gov/ohrp/policy/ohrpregulations.pdf

[2] Appendix M, page3 http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

A NSR (Non-significant Risk) Device Study is one that does not meet the definition for a SR (Significant Risk) device study.[3]

III. MEMBERSHIP

The IRB shall be composed of at least (12) members who are sufficiently qualified to execute the Board's charge based on experience, expertise and diversity of cultural and racial background. Both sexes and more than one profession shall be represented, and at least one member of the Board shall have no other affiliations with Centra Health, Inc.

In addition to possessing the professional competence necessary to review specific investigational activities, the IRB must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable laws, standards of professional conduct and practice, and community attitudes. The IRB must, therefore, include at least one person who shall be a nonscientist and whose concerns are in these areas.[4]

The IRB may also appoint alternate members who may substitute at IRB meetings for absent IRB members provided the alternate's qualifications are comparable to the absent member's qualifications. Alternate members will have all the rights and access to committee materials as other members. Alternate members will only have voting privileges when they are attending meetings in the absence of the member for whom the alternate is substituting.

All IRB members, including alternates, shall be identified by name; earned degrees, if any; position or occupation; representative capacity; and by any other pertinent indications of experience such as Board certification, licenses, etc. sufficient to describe each member's chief anticipated contribution to the IRB's deliberations. Any change in IRB membership shall be reported to the Department of Health and Human Services in such form and at such times as the Secretary of the DHHS may require. IRB membership is recorded on a roster that is submitted to the federal Office for Human Research Protections (OHRP). [5]

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[3] Appendix M, page 3 – Also available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

[4] Reference 21 CFR 56.107(c)

[5] Appendix A

Annually, and whenever a member's interest changes, all IRB members must review and sign the "Centra Institutional Review Board Conflicts of Interest Disclosure Form for IRB Members".[6] The IRB Chairperson shall review all members' Conflicts of Interest Disclosure Forms upon receipt. In the event the Chairperson identifies a potential Conflict of Interest, he may establish an Ad Hoc IRB Conflict of Interest Committee comprised of at least four (4) IRB members to review and make recommendations to the IRB Board as to management of potential conflicts. The Committee will consider whether an actual Conflict of Interest exists, and if so, methods for managing the Conflict of Interest. These may include:

A. public disclosure of "financial interests;"

B. divestiture of significant financial interests;

C. severance of relationships that create actual or potential conflicts;

D. requiring the conflicted Member to leave the room during discussion and voting on the approval of the research.

The Conflict of Interest Committee will make its recommendations to the full IRB for resolution. The Board will determine by majority vote whether the Committee's recommendations provide appropriate safeguards to protect Centra patients and human subjects. If so, a Management Plan will be developed and provided to the individual with the conflict and the Plan will be monitored to ensure compliance by the Conflict of Interest Committee. Whether or not disclosed on an IRB member COI Disclose Form, any Board Member who believes he/she may have a Conflict of Interest with respect to proposed research shall refrain from voting on any matter relating to the study, and he/she may not be present during the final consideration of the application for approval of the research.

Terms. Members will serve staggered terms of three years with no maximum years of consecutive service.

Selection of Members. The Nominating Committee will propose a slate of members to fill Board membership on an annual basis. The annual slate will be voted on by the Board at its annual meeting, and approved by the President/CEO of Centra.[7]

IV. MEETINGS

Regular Meetings. The IRB shall meet monthly on the third Tuesday of each month, which meeting may be rescheduled or cancelled at the discretion of the Chairperson.

Annual Meeting. The annual meeting of the IRB shall be held on the third Tuesday in May, or at such other time as shall be determined by resolution of the Board.

[6] Appendix B; Reference 21CFR.56.107d
[7] VIII.C. of this manual

Special Meetings. Special meetings of the Board may be called by the Chairperson or by at least twenty percent (20%) of the members of the Board.

Quorum. A quorum for a meeting of the IRB shall be a meeting at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. A simple majority of those voting is sufficient for approval of any motion (including, but not limited to, approval of minutes, studies, and amendments to policies and procedures).

Attendance. Members of the Board are expected to attend at least ten (10) of the meetings of the Board each year. Failure to attend at least 10 of the Board meetings may lead to a request by the Board for the member's resignation.

V. OFFICERS

The IRB officers include, but are not limited to: Chairperson, Vice Chair and Secretary. The President/CEO of Centra shall appoint the IRB Officers on an annual basis prior to the IRB annual meeting.

General Duties of Officers. Each of the Officers shall undertake to provide leadership to the IRB. The Chairperson shall be responsible for chairing each of the IRB meetings. In his/her absence, the Vice Chair shall be responsible for chairing such meetings. The Secretary shall be responsible for recording minutes at each IRB meeting, and such other duties as the Chairperson may assign.

VI. IRB RECORD KEEPING

A. The following documentation of the IRB activities will be prepared and maintained (electronic format is acceptable):
   1. Investigational activity proposals including consent forms.
   2. Minutes of meetings.
   3. Records of continuing review.
   4. Copies of correspondence between the IRB and investigators.
   5. A list of IRB members
   6. Written policies and procedures of the IRB.

B. Such documentation for a given study will be maintained for at least three years after completion of the study.[8]

VII. IRB MINUTES

The minutes of the IRB meetings shall include the following:

A. List of members in attendance, members absent, and guest(s) in attendance.
B. Actions.
C. Basis for requiring changes in disapproved investigational activity proposals.
D. A written summary of the discussion of controversial issues and their resolution.

[8] 21CFR §56.115(b)

VIII. IRB COMMITTEES

A. The Executive Committee is a standing committee that meets as needed regarding issues that may arise. Members include:
   1. Chair of the IRB
   2. Vice Chair of the IRB
   3. Secretary of the IRB
   4. Compliance Officer/General Counsel

B. The Policy Committee is a standing committee that meets at least annually and as needed to review and revise the IRB policies and procedures manual. The committee makes recommendations to the full IRB. The IRB considers the recommendation(s) and may approve with a majority vote. The Committee is composed of the following members:
   1. Chairperson of the IRB
   2. Secretary of the IRB
   3. Compliance Officer/General Counsel
   4. Scientific/Clinician Member of the IRB
   5. Two Other IRB Members

C. The Nominating Committee is a standing committee that meets at least annually and as needed to solicit and review nominations for new Board members. The Nominating Committee members include all members of the Executive Committee and one other IRB Member. Nominations for new Board members will be accepted by the Nominating Committee from Board members, peers, and other appropriate leaders within Centra, and candidates will be identified and selected by the Nominating Committee based on criteria for competency.

D. The Exempt Committee is a standing committee of at least two IRB members appointed by the Chairperson of the IRB for purposes of reviewing and evaluating Exempt Research Checklists and confirming that an Application for IRB approval is not required.

E. The Special Resource Committee is tasked with reviewing, evaluating, and advising the IRB regarding the safety and efficacy of a proposed investigational activity. This committee will be appointed by the Chairperson of the IRB when the IRB itself does not possess adequate expertise in the area of the proposed investigational activity.

F. Ad-Hoc Committee: At times the Chairperson of the IRB may appoint ad-hoc committees to consider special items and make recommendations to the Chairperson and/or the IRB.

IX. RELATIONSHIP OF THE IRB TO OTHER COMMITTEES

Any research proposal involving human subjects which will involve the exposure of the patient or medical personnel to an amount of radiation in excess of what they would receive during a routine examination in radiology or nuclear medicine, must be

submitted to the *Radiation Safety and Medical Isotopes Committee* for approval prior to action by the IRB. In involving the use of x-rays or radioisotopes, the IRB will inform the Radiation Safety and Medical Isotopes Committee of its actions by providing copies of the minutes of their meetings. [9]

X. PROCESSING OF APPLICATIONS AND REVIEWER RESPONSIBILITIES

All research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency will be subject to IRB review. All Investigators are required to complete an application applicable to the status of the study. All proposals for investigational activities must be submitted to the IRB at least fourteen (14) days prior to the next meeting for consideration and possible action at that meeting. In general, action on all proposals will be taken within six (6) weeks after submission.

Centra Institutional Review Board **Conflict of Interest** Questions and Certification is required from each Principal Investigator at least annually or if Principal Investigator changes. This form is included in the:

- "Application for IRB approval of Human Subjects Research Form 1" [10]
- "Request for Renewal/Update of IRB Approval Form 2A or Study Closure Form 2B"[11]
- "Modification of Approved Human Subjects Research Form 3" [12]

IRB members shall review and consider Principal Investigator's Conflict of Interest Questions and Certification Forms. In the event any Member identifies a potential Conflict of Interest, he shall bring it to the attention of the Chairperson, and the Chairperson may establish an Ad Hoc IRB Conflict of Interest Committee comprised of at least four (4) IRB members to review all Conflicts of Interest reported by Principal Investigators on the IRB Conflict of Interest Questions and Certification form. The Committee shall make recommendations to the IRB Board as to management of potential conflicts. The Committee will consider whether an actual Conflict of Interest exists and if so, methods for managing the Conflicts of Interest. These may include:

- Public disclosure of "financial interests;"
- Monitoring of research by independent, external reviews;
- Modification of the research plan;
- Disqualification from participation in all or part of the research;
- Divestiture of Significant Financial Interests;
- Severance of relationship that create actual or potential conflicts.

The Conflict of Interest Committee will make its recommendations to the full IRB Board for resolution. The Board will determine by majority vote whether the

[9] Refer to Appendix C, Form 1, Part A.2.18
[10] Appendix C
[11] Appendix D
[12] Appendix E

Committee's recommendation provides appropriate safeguards to protect Centra patients and human subjects. If so, a Management Plan will be developed and provided to the individual with the conflict and the Management Plan will be monitored to ensure compliance by the Conflict of Interest Committee. Non-compliance with the Management Plan shall be grounds for terminating the study.

The IRB will make a risk determination when the sponsor presents a device for investigation as Non-Significant Risk (NSR). Unless the FDA has already made a risk determination for the investigation, the IRB will review the sponsor's NSR determination for each investigational device study reviewed. If the IRB determines that an investigation involves a significant risk devise, presented by the sponsor as NSR, the IRB will notify the investigator and the sponsor of the SR determination.[13]

A letter of decision will be sent by the IRB Chairperson to the Principal Investigator and the study coordinator within five (5) business days of the IRB's vote. The letter shall contain the following:

- Date of decision
- Expiration Date of approval and requirements for renewal(s)
- Explanation of IRB general expectations and any specific requirements
- If a device study, designation of whether the device study is deemed "significant risk" or "non-significant risk"

A. Initial Approval:

1. The Principal Investigator will complete an "Application for IRB approval of Human Subjects Research Form 1." [14] His/Her credentials are to be included in the submission.

2. The Investigator may consult with the Chairperson of the IRB regarding the formation of a Special Resource Committee[15], which will be composed of at least one person qualified to review this investigational activity.
    a. The Chairperson will decide if this proposal must go to a Special Resource Committee or directly to the IRB. If the Proposed investigational activity must go to a Special Resource Committee, the Chairperson of the IRB will appoint the Committee and provide copies of the proposal to the Special Resource Committee Chairperson.
    b. This Committee will recommend either approval or disapproval of the proposed investigational activity. The proposed investigational activity application and the Committee's recommendation shall be forwarded to the Chairperson of the IRB by the Committee.

3. All proposed investigational activities must have the necessary pre-approvals completed and a copy submitted to the Chairperson of the IRB before the next

[13] Appendix M – also available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf
[14] Appendix C
[15] See VIII.e

scheduled meeting of the full Board. The Chairperson of the IRB is responsible for development and distribution of meeting agendas.

4. The Principal Investigator/Sub-Investigator/Study Coordinator will be asked to appear at the IRB meeting to answer any questions about the proposed investigational activity as it pertains to the protection of the rights and welfare of the research subjects.

5. IRB approvals are a period of (1) year, or such other period as determined by the IRB. Approximately thirty (30) days prior to the end of the approval period, the IRB Chairperson will provide in written or electronic notice to the Principal Investigator the following:
   a. the date the study is due to expire,
   b. the date (two weeks prior to the upcoming meeting) the applicable application must be submitted to the Secretary of the IRB, and
   c. the anticipated IRB review date. The investigation may not continue if not approved by the IRB prior to the end of the initial or annual approval period. The Principal Investigator or a Study Coordinator will need to be available either in person or by phone as directed by the IRB Secretary and the IRB Chairman.

B. Other applications include:
   1. Request for Renewal of IRB Approval, Form 2A or Study Closure, Form 2B.[16]
   2. Modification of Approved Human Subjects Research, Form 3.[17] Modifications include changes or additions to the study protocol or informed consent form, change of Principal Investigator.
   3. Reports of Approved Human Subjects Research Form 4.[18]
   4. Protected Health Information: Waiver of Authorization to Perform Human Subjects Research, Form 5. [19]
   5. Exempt Research Checklist, Form 6. [20]
   6. HIPAA Authorization, Form 7.[21]

XI. Other Categories of Review or Reviewers Responsibilities

A. Emergency Use – "Emergency use means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval." [22]

The emergency use of an unapproved investigational drug or biologic requires an IND.[23] If the intended subject does not meet the criteria of an existing study

[16] Appendix D
[17] Appendix E
[18] Appendix F
[19] Appendix G
[20] Appendix H
[21] Appendix I
[22] CFR 56.102(d)
[23] 21 CFR. Part 312

protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug of biologic can be made available for the emergency use under the company's IND. The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article for a specialized use in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means. [24] A similar process is applicable to use experimental devices. [25]

Emergency use of a test article is exempt from IRB requirements, provided that such emergency use is reported to the IRB within five (5) working days and any subsequent use of the test article at the institution is subject to IRB review. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

B. Expedited Review:

In some cases, the Chairman and Vice Chairman may review and unanimously agree to approve an application to renew. If the criteria for expedited review are not met, or if there is not agreement to approve the application, the application must be reviewed by the full board.

The requirements for approval of an application for expedited review of a renewal are as follows:

1. The research is permanently closed to the enrollment of new subjects
2. All subjects have completed all research-related intervention
3. The research remains active only for the purpose of long term follow-up
4. No subjects have been enrolled since the last approval and no additional risks have been identified
5. The remaining research activities are limited to data analysis

All new applications for research involving human subjects are reviewed by the full board.

C. Waiver of Jurisdiction

Local investigators may request a waiver of jurisdiction to another IRB. The investigator seeking a waiver from Centra's IRB should send a letter, or email, to the IRB secretary and should include the following documents:

1. The application that was made to the IRB of record providing review
2. The study protocol
3. The informed consent

[24] 21 CFR. § 312.36
[25] 21 CFR. Part 812

4. A description of the IRB providing review
   Note: A link to a website is sufficient if it provides enough information for the Centra IRB to evaluate.
5. An authorization agreement that delineates the responsibilities of each party, as applicable.

If the investigator provides the documentation referenced above, a Centra IRB application is not required.

The Centra IRB may approve specific reviewing IRBs based on accreditation and other factors. Investigational studies that utilize these IRBs can apply for a waiver of jurisdiction using the expedited review process. If the Chairman and Vice Chairman unanimously approve the request for waiver of jurisdiction in an expedited review, the investigator may proceed without further delay.

The Centra IRB will maintain a list of approved IRBs. The Centra IRB may add or delete from the list. The list must be reviewed at least annually.

If the IRB providing review does not appear on the approved list, the request must be reviewed by the full board.

Investigators who participate in waived investigations are required to report the following information for each study to the IRB annually:

1. Annual total and local enrollment (number of subjects enrolled)
2. Local SAEs reportable to the IRB of record
3. Local protocol deviations and/or violations reportable to the IRB of record

The Centra IRB may approve the use of another IRB in cases where an academic institution allows a local investigator to enroll Centra patients, but will not otherwise provide a reliance agreement to the Centra IRB. This is not a "waived" study per se, and the IRB at the institution has no responsibility to the Centra IRB. However, the local investigator continues to be responsible for reporting to the Centra IRB and the Centra IRB will have the authority to discontinue local enrollment. The local investigator will be required to report the same information as other investigators who report on waived studies.

D. Lapsed Studies

All studies expire at midnight on the expiration date. Once the approval period for a given study has expired without renewal it is considered a lapsed study and investigators must stop all research activities involving human subjects except where doing so would jeopardize the welfare of the subject. All enrollments must cease along with continuation of research interventions or interactions with currently participating subjects and data analysis of identifiable private information.

The IRB Chairperson will send a written notice within two (2) days of the lapse notifying the principal investigator that the IRB approval has expired.

When a protocol is lapsed, the Investigator must stop all activity on the protocol, including subject recruitment and enrollment, procedures, and analysis and/or publication of exiting data.
If withdrawal of current participants from the research is necessary, the Investigator will be required to:

A. Inform enrolled participants that the study has lapsed; and
B. Develop procedures for withdrawal that protect the rights, safety, and welfare of participants, and describe those procedures to participants.

The Principal Investigator may apply for a renewal following the lapse and the IRB will review the application at the next meeting. If approved, the study may resume. The IRB cannot retrospectively grant approval to cover a period of lapsed IRB approval.

E. Suspension or Termination of a Study by the IRB

Definitions:

Suspension: All project activities must cease until any pending issues can be resolved satisfactorily. Suspended studies are still approved, but in a 'hold' status until the pending issues can be resolved.

Termination: The study is no longer approved. All project activities must cease immediately, including data analysis and any resulting data or analysis is null and void. A study may be terminated by the IRB or by the sponsor for administrative, regulatory or other reasons (such as initial study results). Regardless of the reason, terminated studies are not considered completed.

Closure: This is an administrative status whereby a previously approved protocol's expiration date has passed and an investigator has not submitted a renewal, or the investigator has submitted a study closure request. The IRB assumes that no human subject research activities are ongoing and, for administrative record keeping, the study record is closed.

The IRB shall have authority to suspend or terminate approval or research that is not being conducted in accordance with federal and state regulations, IRB requirements, or research that has been associated with unexpected serious harm to subjects (45 CFR 46.113). A research project may be suspended or terminated for a variety of reasons, including *but not limited to:*

1. Serious adverse event(s) and unanticipated problem(s)
2. Detrimental change in the risk-benefit ratio of the study
3. Conduct of research activities without prior IRB approval
4. Failure to obtain appropriate consent
5. Failure of investigators to complete required training
6. Other noncompliance issues

Upon termination of a study, the IRB Chairperson shall include a statement of the reasons for the IRB's action and promptly report the termination to the OHRP, the regional office of the FDA, and other regulatory bodies as indicated. The report will give the reasons for termination and the effective date.

Suspension and termination process and notification:

- When potential cause for further investigation is demonstrated, an inquiry into the specific circumstances giving rise to concern with a specific protocol will be conducted. If a protocol is determined not be in noncompliance or a detrimental changed in the risk/benefit occurs, further action will be taken by the IRB.
- In most cases, the IRB will review the circumstances of the case and make a determination of suspension or need for termination. Other IRB members may be consulted as needed in the decision making process leading up to bringing the issue to the full committee.
- In emergency situations, the IRB Chair in consultation with an IRB Vice Chair, will make a determination of the need to suspend or terminate a study immediately.
- The IRB Chair (or his or her designee) will write a letter that includes the following:
    1. A description of the event
    2. The determination of the IRB (i.e. suspension, termination)
    3. Justification for the determination
    4. Requirements of the investigator (e.g. cease all data collection)

  The letter will be forwarded to the Investigator, any Sponsor(s), and applicable federal agencies (E.g. FDA, OHRP-Office for Human Research Protection). A Copy of the form is filed with the protocol's IRB file.

- The Lead Investigator is responsible of notifying (in a timely manner) all co-investigators, key personnel, and other research staff associated with the protocol as well as any subcontract grantees if the protocol has been suspended or terminated.

Participant Involvement in Suspended or Terminated Protocols

When a protocol is suspended or terminated, the Investigator must stop all activity on the protocol, including subject recruitment and enrollment, procedures, and analysis and/or publication of exiting data.

When the suspension or termination of a research protocol involves the withdrawal of current participants from the research, the Investigator will be required to:

1. Inform enrolled participants that the study has been suspended or terminated; and
2. Develop procedures for withdrawal that protect the rights, safety, and welfare of participants, and describe those procedures to participants.

In certain circumstances, project activities may continue if stopping study procedures/ treatment will adversely affect the welfare of a subject. If the suspension or termination of a research protocol does involve the withdrawal of current participants from the research, the Investigator will be required to:

1. Notify the OHRP immediately of the need to continue any procedures/ treatment;
2. Inform enrolled participants that the study has been suspended or terminated; and,

3. Report any serious adverse events or unanticipated problems involving risks to participants to the IRB.

Reinstatement of Suspended or Terminated Protocols

Suspended Studies: To reinstate a project that has been suspended, the investigator must resolve satisfactorily any pending issues as required by the IRB. After one year of suspension or the expiration date of the study (whichever comes first), if adequate progress has not been made on the pending issues then the IRB will administratively close the study protocol.

To reinstate a project that has been suspended the investigator must contact the OPHS in writing within 30 days of the suspension. The investigator must address the following in a letter:

1. Reason for requesting the study be reinstated.
2. Short summary of the purpose of the study and intended objectives/outcomes. This may be incorporated into the protocol narrative noting any changes, revisions or clarification.
3. Description of how the study has changed, if any, since initial approval using the appropriate Amendment form and procedure for identifying changes in the protocol narrative.
4. Summary of status of the study, including:
   a. How many subjects were enrolled;
   b. At what point in the treatment/procedures were the subjects at the time of suspension;
   c. Any adverse events or amendments since last continuing review, including a description of each;
   d. Any additional relevant information.
5. Documented plan to ensure that reason for suspension will not happen again and that the study will be in compliance with all applicable laws and regulations
6. Anticipated enrollment, if the study is reactivate
7. In the case that IRB-approval of a protocol is reinstated, the IRB may require that subjects who were previously enrolled be re-consented.

Terminated Studies. Terminated studies may be reinstated or reactivated with appropriate modifications to address the reason(s) the study was terminated. Investigators will need to submit a completely new application if they wish to resume a terminated study.

F. Exempt

Exempt Research Checklist (Form 6) will be submitted to the Exempt Committee for consideration and confirmation that an application to the IRB is not required. If not approved as Exempt, an Initial Application (Form 1) will need to be submitted.[26]

G. Miscellaneous

For requests not otherwise defined above, the IRB Board has the authority to meet and consider such requests at the discretion of the Chairperson.

[26] See X.A. and Appendix C of this manual

XII. INFORMED CONSENT

The IRB shall be charged with the safeguarding of the rights and welfare of subjects at risk in investigational activities supported by the IRB of Centra Health, Inc. No investigational activity involving human subjects shall be undertaken unless the IRB has reviewed and approved such investigational activity. This review will evaluate the relative risks and benefits and will require a legally effective informed consent as outlined by both the FDA and the HHS to be obtained and documented. Specific attention should be paid to Guidelines for Informed Consent as contained in federal regulations. Specific attention should be given to paragraph *21 CFR Section 50.25*[27] which outlines the elements of informed consent.

A. In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research, an explanation of the purposes of the research and the duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others which may reasonable be expected form the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extend, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
6. 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.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
8. 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.

B. Additional elements of informed consent: When appropriate, one or more of the following elements of information shall also be provided to each subject:

1. 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.
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

[27] 21 CFR Section 50.25

3. Any additional costs to the subject that may result from participation in the research.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation
6. The approximate number of subjects involved in the study.

C. When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j) (l) (A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this web site at any time."

D. Consent process:

1. No investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.
2. An investigator shall seek such 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.
3. The information that is given to the subject or representative shall be in language understandable to the subject or the representative.
4. No informed consent, whether oral or written, may include any exculpatory 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.

E. Vulnerable population include:

1. Pregnant Females and Fetuses – Because of the inherent danger to fetuses of some investigational activities, use of women to child-bearing age or women known to be pregnant is specifically discouraged, unless it is clearly evident that no potential danger to the fetus exists. The Principal Investigator shall make it his responsibility to inform the research subjects that they should not become pregnant during the research project and should they become pregnant they will be eliminated from the study.
2. Prisoners – Investigational activities using prisoners must be in compliance with both FDA and HHS regulations. Any investigational activity involving prisoners will necessitate a review by a Special IRB which includes a prisoner advocate. This IRB will be constituted of the regular Centra Health, Incorporated IRB plus the prisoner advocate.

3. Children and the Individuals with Mental Disabilities – The use of children (subjects less than 18 years of age) or those who are individuals with mental disabilities (subjects whose mental age is less than 18 years) is discouraged unless there are no reasonable alternatives. It is recommended that investigators consider the use of adults or animals in preference to children whenever possible. All investigational activities using subjects less than legal age will require informed consent from the parents or guardians of the subject children. Individuals with mental disabilities must have informed consent obtained from parents or legal guardians, and in the case where parents are unavailable such as in the situation where the subject is in foster care or in another institutional setting, there will be an officially designated representative for the individuals with mental disabilities. In situations where the mental age is greater than 12 years (subjects who are either individual with mental disabilities disabled or minor children) the assent of the subject will also be obtained in addition to the informed consent and permission of the parent or guardian. If the investigational activity presents substantial risk to the subjects and there is substantial reason to believe that the parents or legal guardians of investigational activity subjects may be unable to consider adequately their child or ward's interest in determining whether to consent to participate in the investigational activity, an advocate shall be appointed to review the case of each child and to decide whether it is in the child's interest to participate. If an advocate is appointed, his or her consent must be obtained as well as that of the parent or guardian and the subject (where applicable).

XIII. CRITERIA FOR DENYING APPROVAL

Any proposed research activity will be denied if any of the following conditions apply:

A. The proposed research activity violates laws or regulations established by the Federal Government, the Commonwealth of Virginia or Centra Health, Incorporated.

B. If, in the judgment of the IRB, the risk created to the subjects outweighs the benefits to be obtained.

C. If, in the process of conducting an investigational activity, unnecessary risks are imposed, the investigational activity will be disapproved. In this regard, it is expected that all investigational activities involving human subjects will attempt to minimize the amount of risk imposed as outlined in the federal regulations.

D. In the IRB's judgment there is insufficient Informed Consent.

E. The IRB judges that payment or other offered inducements are likely to unduly influence subjects and/or investigators.

XIV. COMPLIANCE

Definitions:

Non-compliance – non-compliance with the regulations or the requirements of determinations of the IRB.

Serious Non-compliance – Any non-compliance that results in harm to subjects, or poses a risk of harm to subjects. Examples include conducting human subjects research

without IRB approval; failure to obtain informed consent prior to a participant's involvement in research.

Continuing Non-compliance – Any event that in singular does not constitute non-compliance, but in aggregate does. Examples include a PI misses a continuing review deadline three years in a row; a PI has multiple studies with the IRB and misses more than three deadlines.

It is the responsibility of the IRB to monitor compliance with protocols for investigational activities to protect the rights of human subjects and ensure compliance with the requirements and determinations of the IRB.

Non-compliance may be discovered in a number of ways, including investigator monitoring, complaints, protocol deviations, and reports by PIs to the Board. All concerns about non-compliance should be reported to any member of the IRB who will report the information to the IRB Chair. Reports of non-compliance may be made by email, telephone or in person (question: do we have an IRB website whereby folks could report?). Anytime the IRB becomes aware of possible non-compliance and determines that an investigation is warranted, the IRB Chair may appoint a subcommittee to review the allegations of non-compliance and conduct an investigation. The subcommittee will meet, collect information about the allegations of non-compliance, triage the information, and determine whether non-compliance occurred. If non-compliance occurred, the subcommittee will also consider and determine whether the non-compliance is serious or continuing. If the subcommittee determines that non-compliance has occurred but it was neither serious nor continuing, the subcommittee will recommend steps to be taken to address the issue and prevent such non-compliance in the future. If the subcommittee determines serious or continuing non-compliance has occurred, the information will be presented to the IRB for discussion and final determination as to what action is appropriate.

Once the IRB has heard the subcommittee's report, it will discuss and determine next steps. The IRB may take any number of actions in response to reports of non-compliance, keeping in mind that its duty is to protect human research subjects. Actions which may be taken by the IRB include, but are not limited to, educating the investigator and/or research staff, suspending or terminating the research, suspending the investigator, notifying participants, modifying the protocol and/or consent, monitoring the research, requiring continuing review more frequently than once a year, conducting random audits of the investigator, and modifying or suspending other protocols in the event the non-compliant PI has more than one study.

Anytime the IRB makes a determination of serious or continuing non-compliance, the IRB Chair will report such non-compliance to the ORHP or the FDA by summarizing the investigation and basis for the determination, and submitting that summary in writing within 30 days of the IRB's determination, or sooner as required given the circumstances.

For serious or continuing noncompliance, reports to regulatory agencies will include:

A. Name of the institution conducting the research;
B. Title of the research project in which the noncompliance occurred, or for IRB or institutional noncompliance, the IRB or institution involved;

C. Name of the principal investigator on the protocol;
D. Number of the research project assigned by the IRB and the number of any applicable federal award(s);
E. A detailed description of the noncompliance;
F. Actions the institution is taking or plans to take to address the noncompliance.

INVESTIGATOR COMPLIANCE

It is the responsibility of the IRB to monitor compliance with protocols for investigational activities to protect the rights of human subjects. It will be the responsibility of the IRB to recommend the frequency and method for monitoring all investigational activities to assure investigator compliance. Such monitoring will focus specifically on changes in study protocol and obtaining and documenting informed consent. At the time of approval of an investigational activity, the IRB will establish a schedule for conducting continuing review of the research and investigational activities that are the subject of the approval. Such reviews will be scheduled to occur and must occur no less frequently than annually.

Monitoring and documenting investigator compliance falls into three major categories:

A. Business monitoring to be accomplished by submission of the annual renewal application assuring no changes in protocol or untoward effects occurring within human subjects.

B. Interim reports to the IRB will be made during the course of the investigational activity, as required by law, documenting any changes in the protocol or any unanticipated events occurring in a human subject. Interim reports must be made in writing at the time of occurrence to the Chairperson of the IRB or his/her designee. Copies of the report shall be distributed to all IRB members and kept on file. Changes to any protocol cannot be initiated without the approval of the IRB.

C. Reviews will be scheduled at more frequent intervals than annually if the IRB determines that the degree of risk of the approved research and investigational activity warrants such more frequent review. Special monitoring procedures for high risk or other projects as deemed necessary by the IRB which will be determined at the time of approval. Specific mechanisms for monitoring both informed consent and protocol adherence will note the frequency and method by which monitoring is to be accomplished and the individual(s) who is/are responsible for such monitoring activities.

XV. REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS TO THE IRB

Federal regulations require investigators to report to the IRB any unanticipated problems involving risks to subjects or others. It is important to understand the difference between “adverse events” and “unanticipated problems” because many adverse events are not reportable.

A. "Adverse event" or "adverse experience" is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding) symptom, or disease, temporarily associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms and occur most frequently in the context of biomedical research, although they can occur in the context of social and behavioral research.

B. "Serious Adverse Event" (SAE) is any adverse event associated with the subject's participation in research that meets any of the following criteria:

1. results in death;

2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);

3. requires hospitalization or prolongation of existing hospitalization;

4. results in persistent or significant disability/incapacity;

5. results in a congenital anomaly/birth defect;

6. any other adverse event that, 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 this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

C. "Unexpected Adverse Event" is any adverse event, the specificity or severity of which is not consistent with the current investigators brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current research application, as amended.

D. "Unanticipated Problem" (UP) The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the federal regulations at *45 CFR part 46*.[28] Federal guidance considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following 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 the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

[28] 45 CFR part 46

2. related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Federal guidance recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. It notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

1. changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;

2. modification of inclusion or exclusion criteria to mitigate the newly identified risks;

3. implementation of additional procedures for monitoring subjects;

4. suspension of enrollment of new subjects;

5. suspension of research procedures in currently enrolled subjects;

6. modification of informed consent documents to include a description of newly recognized risks; and

7. provision of additional information about newly recognized risks to previously enrolled subjects.

E. Investigators must report SAEs and UPs to the IRB within five (5) business days of knowledge of the event from the sponsor. Reports must be made to the IRB. The report to the IRB must include the name of the research project in which the reportable incident occurred; name of the principal investigator on the protocol; number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement) if any; a detailed description of the problem; and actions proposed or being taken or planned to be taken to address the reportable incident (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.), and

confirmation that the event has been reported in accordance with section XV. [29] of this manual.

F. Investigators must report local SAEs and UPs to the IRB within five (5) business days of knowledge of the event. Reports must be made to the IRB Chairperson. The report to the IRB must include the name of the research project in which the reportable incident occurred; name of the principal investigator on the protocol; number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement) if any; a detailed description of the problem; and actions proposed or being taken or planned to be taken to address the reportable incident (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.), and confirmation that the event has been reported in accordance with section XV.[30] of this manual. If the IRB Chairperson disagrees with the action taken by the Principal Investigator or study coordinator, the IRB Chairperson may suspend the study and convene a committee or call a special meeting of the IRB to review the matter.

G. Pursuant to federal regulations and federal guidance, the IRB will advise that the Principal Investigator or study coordinator will report SAEs and UPs to OHRP **and the regional office of the Food and Drug Administration** as appropriate**.** The report will include Centra Health, Inc. as the name of the institution conducting the research; title of the research project and/or grant proposal in which the problem occurred; name of the principal investigator on the protocol; number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement) if any; a detailed description of the problem; and actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.).

XVI. NOTIFICATION

Following any vote by the IRB or significant discussion as to protocol pertaining to a particular study, the IRB Chairperson will notify in writing the Principal Investigator and study coordinator of the IRB's action, including any particular finding(s) or concern(s). Such notice should be provided within five (5) business days following the IRB meeting at which the vote, action or discussion took place.

XVII. CONFIDENTIALITY

It is the responsibility of each Principal Investigator to give written assurance at the time of application to the IRB that subject confidentiality will be protected. Implicit statements or confidentiality protection are not sufficient and some explicit acknowledgements and description of the method by which sensitive human data will be protected are required.

[29] Section XV. of this manual
[30] Section XV. of this manual

XVIII. COMPENSATION OF SUBJECTS

While it is acceptable to compensate subjects for discomfort or inconvenience resulting from their participation in investigational activities, investigators must not offer undue inducements in recruiting subjects. Compensation may take the form of monetary payments, reduced or waived fees for diagnostic or therapeutic services. In no case should an offer of compensation constitute inducement to take risk, nor should the amount of compensation be based on any degree of risk. Where risk is minimal or very low, and subjects expect no medical benefits to themselves to result from participation in investigational activities, it is reasonable for the investigator to offer compensation which does not exceed in value the equivalent of the subject's expenses plus a fair wage for the subject's time, inconvenience and discomfort.

Where subjects may be expected to gain some medical benefits from participating in an investigational activity, or where subjects may undergo more than very low risk, compensation should not exceed the value of actual expenses or losses incurred by subjects as a result of their participation. Investigators should take care when recruiting patients not to take advantage of populations likely to be unduly influenced by the form of compensation offered. If compensation is offered, the investigator must:

A. Explain the nature of compensation and the basis for offering (if compensation is to be pro-rated for subjects completing only part of the study, the basis for pro-rating should be explained).

B. State how subjects to be compensated will be recruited.

C. Include in the consent form a description of the nature of the compensation and, if applicable, the basis for pro-rating compensation for subjects who fail to complete their participation in the investigational activity.

XIX. IRB OBSERVATION

In order to monitor Principal Investigator compliance with IRB policy or federal and/or state regulatory requirements, the IRB reserves the right to appoint one or more of its members or a designated third party to observe any activity under the approved study, particularly pertaining to consent process and/or research. Such observation may be carried out at the discretion of the IRB. Any refusal by a Principal Investigator or study coordinator to an IRB request for observation will be grounds for the imposition of sanctions by the IRB, including suspension and/or termination of the study.

Appendices