

The Carle Foundation
IRB Policy 403

Subject	Modifications to Previously Approved Research			
Approval	Apr 2011	Review		Revision
Purpose	To inform the Principal Investigator that the Carle Institutional Review Board (Carle IRB) requires that any modification of Carle IRB approved research must be submitted for review and approval by the IRB prior to continuation of the research.			

Statement of Policy

1. Any proposed modifications, amendments, revisions, changes or additions in procedures, alterations of risk compared to the currently approved protocol, or changes in subject population, must be reviewed and approved by the Carle IRB prior to continuation of the research. Prior approval by the Carle IRB is required except when necessary to eliminate apparent immediate hazards to the subject (21 CFR 56.108(a)(4) and 45 CFR 46.103 (b)(4)(iii)).
2. Principal Investigators may not initiate any changes in research procedures or consent form(s) without prior Carle IRB review and approval. Examples of modifications that require Carle IRB review include, but are not limited to, changes in:
 - a. Study personnel;
 - b. Advertising materials (flyers, radio spots, etc.);
 - c. Research procedures;
 - d. Subject populations (e.g., inclusion or exclusion criteria);
 - e. Location where research will be conducted;
 - f. Consent form (including translations);
 - g. Recruitment procedures;
 - h. Study design or methods; or
 - i. Alterations of risk compared to the currently approved protocol.
3. If changes are made to the protocol without prior IRB approval to eliminate apparent hazards to the subject(s), investigators must promptly report the changes to the Carle IRB using Prompt Reporting Form for review and determination as to:
 - a. Whether any of the required determinations change in any way and
 - b. Whether it was consistent with ensuring the participants' continued welfare and
 - c. Whether the protocol continues to satisfy requirements for IRB approval under HHS/FDA/VA regulations as applicable.
4. Investigators must promptly notify the Carle IRB in writing of any change in a protocol's status, such as discontinuation or completion of a study. See the Carle IRB Continuing Review Policy 404 and Project Closure or Transfer Policy 405.

Definitions

The Carle Foundation – Includes all legal entities part of The Carle Foundation such as Carle Foundation Hospital, Carle Physician Group, Mills Breast Cancer Institute, and Carle Cancer Center.

The Carle IRB – The Internal IRB to The Carle Foundation.

Key Research Personnel – Investigators and other individuals who contribute to the scientific development or execution of a research study or research project in a substantive, measurable way, whether or not they receive salaries or compensation under the grant. These individuals participate in the conduct, reporting, supervision and management of human subject research.

Principal Investigator – The investigator/ researcher who is responsible for the conduct of a research study at an institutional site.

Procedures

1. The Principal Investigator shall submit to the Carle IRB all proposed modifications using the Modification Request Form as well as a “clean copy” and a “tracked changes” copy of each document modified in order to clearly show the IRB what changes are proposed. Only the modified study document(s) needs to be included in the submission.
2. The Principal Investigator shall assess whether the proposed modification will change the risk/benefit ratio and/or require the currently active subjects to undergo any new or revised procedures. In either case, the Investigator shall submit a revised consent form in order to re-consent currently active subjects if those subjects are to undergo any new or revised procedures.
3. The Principal Investigator shall submit to the Carle IRB any proposed changes to non-exempt research as well as to research previously determined by the Carle IRB to be exempt so that the IRB can determine if the proposed changes

modify the previous exempt determination. .

4. If the Principal Investigator has modified research activity without Carle IRB approval to avoid apparent immediate hazards to the subject, the modifications shall be promptly reported to the Carle IRB using the Prompt Reporting Form. In accordance with IRB Policy 801, the Carle IRB will review all changes to approved research initiated without IRB approval to eliminate apparent immediate hazards to the participants, to determine whether the change are consistent with ensuring the participants' continued welfare.

Review Type

The IRB may use the expedited review procedure to review minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Proposed modifications to research originally reviewed at a full board review are also reviewed at a convened IRB meeting unless found to be minor, as defined below.

Proposed modifications to research previously approved via expedited review may also be reviewed by expedited review unless the change results in the research activity no longer meeting the conditions for expedited review. In this case, the proposed modification will be referred to a convened IRB for review.

In all cases, the modifications are reviewed by the IRB Chair or designee (hereafter the "Expedited Reviewer"). The Expedited Reviewer shall document on the Expedited Reviewer Checklist reviewer checklist the determination regarding whether the convened IRB or expedited review procedures are appropriate.

For research that was initially approved by the convened IRB, a minor change is a modification which in the judgment of the reviewer does not fundamentally alter the judgments relied upon to make determinations on any of the criteria for IRB approval under 45 CFR 46.111. The following examples are provided but do not encompass the entire spectrum of modifications that may be proposed to the Carle IRB:

Area of study affected by modification	Examples of minor change	Example of major changes
Elements of consent	<ul style="list-style-type: none"> -- Changes to improve the clarity of statements or to correct typographical errors, provided that such a change does not alter the content or intent of the statement; -- Addition of safety information limited to non-serious risks; 	<ul style="list-style-type: none"> -- Alter or waive informed consent; -- Use of surrogate consent for incapacitated or incompetent adult subjects; -- Addition of new safety information that will directly affect the subjects willingness to participate (e.g., new unanticipated problems involving risks)
IRB Approval 46.111 – Risks minimized	<ul style="list-style-type: none"> -- Clarification of risks without changing the expected nature, severity or frequency of risks; -- Add a new risk to existing procedures that is considered not serious; -- Addition of research activities that would be considered exempt or expedited if considered independent from the main research protocol; -- Modification of the study design that will not change or will reduce the likelihood or magnitude of harm while still addressing the purpose (e.g., increase hospital stay to improve safety monitoring); -- Modification of the study population that will not change or will reduce the likelihood or magnitude of harm while still addressing the purpose (e.g., broaden exclusion 	<ul style="list-style-type: none"> -- Add a new procedure with an expected serious harm; -- Add a new risk to existing procedures that is considered serious; -- Change in severity of an expected risk from not serious to serious; -- An increase in the incidence of an expected serious risk (either from rare to likely or less likely or less likely to likely); -- Modification of the study design that will increase the likelihood or magnitude of harm; -- Modification of the study population that will increase the likelihood or magnitude of harm; -- Modification of a study procedure that will increase the likelihood or magnitude of harm;

	criteria or narrow inclusion criteria); -- Modification of a study procedure that will not change or will reduce the likelihood or magnitude of harm while still addressing the purpose (e.g., reduce the number procedures or reduce amount collected or administered);	
IRB Approval 46.111 – Risks reasonable relative to benefits	-- Modifications with no affect on the risks or benefits -- Modifications that improved the acceptability of the risks in relation to the harms; -- Addition of a direct benefit to the subjects enrolled;	-- Modifications that worsen the acceptability of the risks in relation to the harms; -- Removal of a direct benefit to the subjects enrolled;
IRB Approval 46.111 – equitable selection of subjects	-- Addition/modification of recruitment procedures or materials; -- Addition/modification of payments to subjects that will not unduly influence the subject; -- Addition of children under 46.404;	-- Addition of children under 46.405 – 408; -- Addition of a pregnancy women/fetus population; -- Addition of a prisoner population;
IRB Approval 46.111 – adequate safety monitoring	-- Addition/modification of safety monitoring plan that will likely improve the safety of subjects;	-- Modifications to the safety monitoring plan that will reduce the current protections;
IRB Approval 46.111 – adequate protection of privacy and maintenance of confidentiality	-- Addition/modification of privacy or confidentiality safeguards that will likely improve the protections;	-- Modifications to the privacy or confidentiality safeguards that will reduce the current protections;
Qualification of the research team	-- Changes in study staff; -- Additional training or changes to scope of practice	-- Suspension/lapse of investigator privileges that directly reflect research procedures; -- New disclosures of conflict of interest
Facilities available to support safe conduct of the study	-- Changes in study sites	-- Withdraw of institution/staff support for research that directly affects safe conduct of research;

Note: Changes which, in the opinion of the Expedited Reviewer do not meet the criteria or intent of a minor modification, will be forwarded to the convened Carle IRB for review.

For expedited research that was initially approved by expedited review, a minor change is a modification that does not change the study's eligibility for expedited review. The following examples are provided:

Examples of minor changes	Example of major changes
-- Modifications that are minimal risk and fit within the expedited review categories 1 – 7 -- Addition of research activities that would be considered exempt or expedited if considered independent from the main research protocol	-- Modifications that are greater than minimal risk (e.g., addition of anesthesia or ionizing radiation; -- Modifications that do not fit within the expedited review categories;

If the Expedited Reviewer determines the changes are minor, then the reviewer follows the expedited procedures listed below.

Note: If the Expedited Reviewer determines the changes are not minor, the Reviewer forwards the proposed modifications to HSP staff in order to initiate the review of the proposed modifications by the convened Carle IRB.

Expedited Review of Proposed Modifications to Approved Research

The Expedited Reviewer conducts the review, using standard expedited review procedures as detailed in Carle IRB Policy 401—Expedited Review. The IRB membership is notified of the expedited approval by providing the IRB Agenda Report to

the members of IRB as part of each convened meeting's agenda. During the meeting, the members are reminded that they can request additional information related to the expedited approvals.

Rather than completing the entire Reviewer's Worksheet for Research Study, the Expedited Reviewer documents review and approval of the proposed modifications using the Expedited Reviewer's Checklist. If the Expedited Reviewer determines that the proposed changes are not minor and must be reviewed by the convened IRB, the Primary Reviewer will complete the Reviewer's Worksheet for Research Study prior to the convened meeting at which the proposed modifications are reviewed.

Full Board Procedures

When a proposed change in research study is not minor or could possibly introduce increased risk to study participants or might adversely affect the willingness of current participants to remain in the study, then the Carle IRB must review and approve changes at a convened meeting before changes can be implemented. The Principal Investigator may be invited to attend the meeting if the modification is unusually complex, if the staff anticipates a controverted issue will arise during the review, or at the request of an IRB member.

A Primary Reviewer will be designated for reviewing the proposed modification, determining whether the modified research continues to fulfill the criteria for IRB approval as detailed in Carle IRB Policy 402 and documenting his/her determinations on the Reviewer's Worksheet for Research Study. The Primary Reviewer leads the IRB's review of the proposed modifications and provides his/her recommendations to the IRB at the convened meeting. **Review Outcomes**

For expedited review of proposed modifications, the outcomes of review are the same as those outlined in IRB Policy 401—Expedited Review. For convened IRB review of proposed modifications, the outcomes of review are the same as the options outlined Carle IRB Policy 406--Categories of Action and Communication the Carle IRB's Decision to the Principal Investigator.

If the modification involves the addition of new study personnel who have not completed the mandatory IRB training, the IRB will not approve the addition of these persons as study personnel until they have submitted proof of training unless the **Expedited Reviewer or convened** IRB determines that the study personnel's role in the research is minor as noted in Carle Research Institute Policy 102—Education Requirements for Investigators and Key Personnel Involved in Research. If the IRB approves the modification, the end date of the approval period remains the same as that assigned at initial or continuing review unless the IRB specifically shortens the current approval period (requiring continuing review earlier) as part of the motion voted on by the members.

If a modification request is submitted with a continuing review, the Principal Investigator will receive a written notification of IRB approval or disapproval of the modification request separate from the IRB continuation review determination letter.

If the Principal Investigator has concerns regarding the IRB decision, he/she may submit his/her concerns to the IRB in a written document that includes a justification for changing the IRB decision.

References

45 CFR 46.103(b)(4)
45 CFR 45.110(b)(2)
21 CFR 56.108(a)(3) and (4)
21 CFR 56.110(b)(2)

Electronic Approval on File

Supersedes Carle IRB Policy 403 Ongoing Oversight

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