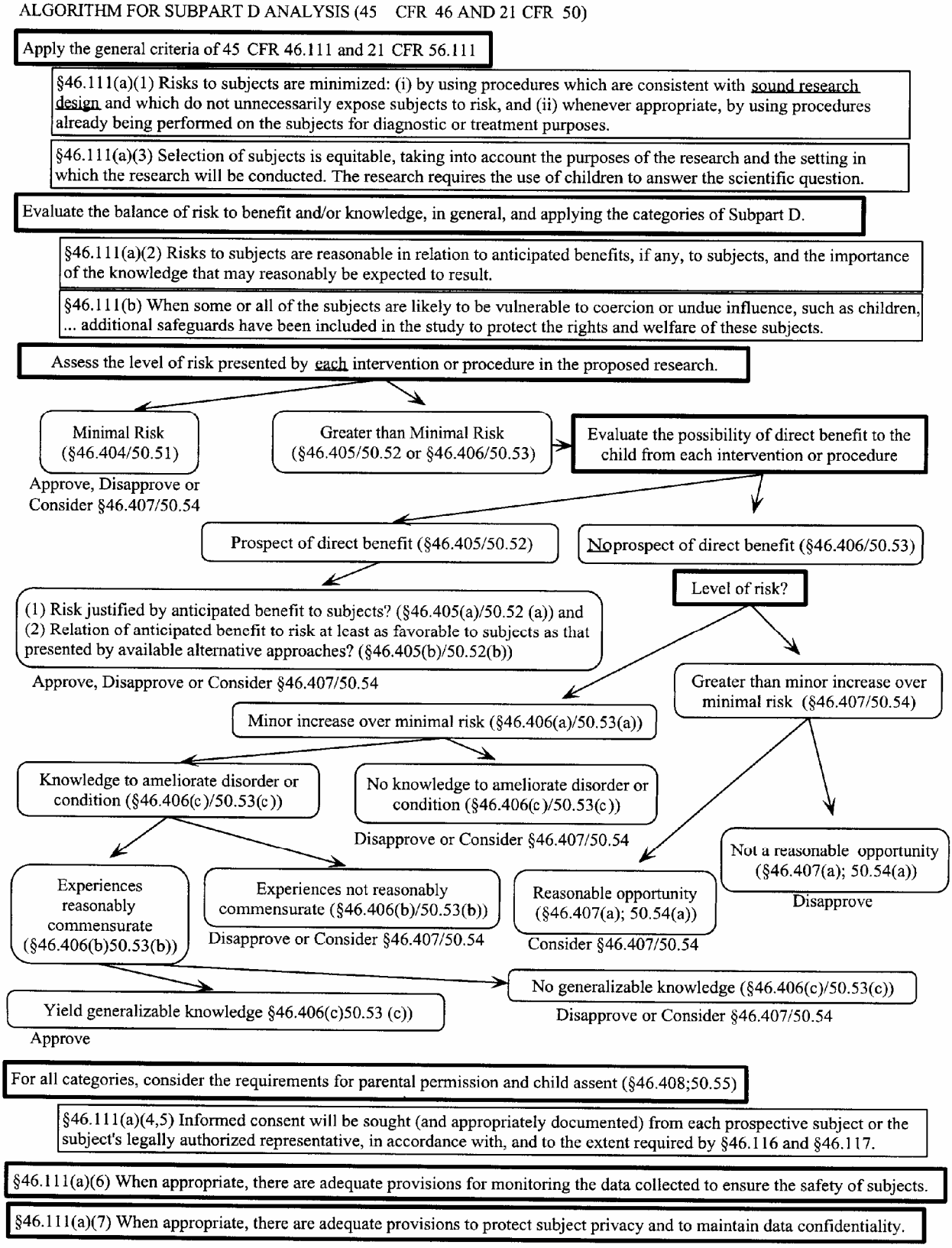
Appendix A


ALGORITHM FOR SUBPART D ANALYSIS (45 CFR 46 AND 21 CFR 50)
Apply the general criteria of 45 CFR 46.111 and 21 CFR 56.111
§46.111(a)(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.
§46.111(a)(3) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which the research will be conducted. The research requires the use of children to answer the scientific question.
Evaluate the balance of risk to benefit and/or knowledge, in general, and applying the categories of Subpart D.
§46.111(a)(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.
§46.111(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, ... additional safeguards have been included in the study to protect the rights and welfare of these subjects.
Assess the level of risk presented by each intervention or procedure in the proposed research.
Minimal Risk (§46.404/50.51)
Approve, Disapprove or Consider §46.407/50.54
Greater than Minimal Risk (§46.405/50.52 or §46.406/50.53)
Evaluate the possibility of direct benefit to the child from each intervention or procedure
Prospect of direct benefit (§46.405/50.52)
Noprospect of direct benefit (§46.406/50.53)
(1) Risk justified by anticipated benefit to subjects? (§46.405(a)/50.52 (a)) and (2) Relation of anticipated benefit to risk at least as favorable to subjects as that presented by available alternative approaches? (§46.405(b)/50.52(b))
Approve, Disapprove or Consider §46.407/50.54
Level of risk?
Minor increase over minimal risk (§46.406(a)/50.53(a))
Greater than minor increase over minimal risk (§46.407/50.54)
Knowledge to ameliorate disorder or condition (§46.406(c)/50.53(c))
No knowledge to ameliorate disorder or condition (§46.406(c)/50.53(c))
Disapprove or Consider §46.407/50.54
Not a reasonable opportunity (§46.407(a); 50.54(a))
Disapprove
Experiences reasonably commensurate (§46.406(b)50.53(b))
Experiences not reasonably commensurate (§46.406(b)/50.53(b))
Disapprove or Consider §46.407/50.54
Reasonable opportunity (§46.407(a); 50.54(a))
Consider §46.407/50.54
No generalizable knowledge (§46.406(c)/50.53(c))
Disapprove or Consider §46.407/50.54
Yield generalizable knowledge §46.406(c)50.53 (c))
Approve
For all categories, consider the requirements for parental permission and child assent (§46.408;50.55)
§46.111(a)(4,5) Informed consent will be sought (and appropriately documented) from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116 and §46.117.
§46.111(a)(6) When appropriate, there are adequate provisions for monitoring the data collected to ensure the safety of subjects.
§46.111(a)(7) When appropriate, there are adequate provisions to protect subject privacy and to maintain data confidentiality.

Appendix B

Non-FAC Open Panel Model Guidelines

1) Only OHRP screened applications which meet the requirements for review under the 407 process are forwarded for review by the panel of expert consultants.

2) Relevant protocol and IRB documents are posted on the OHRP website for public review and a Federal Register notice is prepared that:
    a) Invites public review and comment on the proposed research; and
    b) Announces the date on which the panel of expert consultants will be convened and invites members of the public to attend.

3) Expert consultants selected from a standing pool of experts, supplemented with appropriate protocol specific experts, receive protocol materials and public comments for review.

4) Experts new to the expert panel consultation review process receive an appropriate orientation by OHRP staff.

5) A face-to-face meeting of the expert consultants is convened, with the public present for a portion of the meeting.

6) All experts are given an opportunity to express their opinions, review all materials, and listen to public comments.

7) After their convened meeting and consideration of public comments, each expert consultant writes an independent recommendation regarding the proposed research.

8) The individual reports from the expert consultants are posted on the OHRP website.

9) OHRP develops recommendations based upon all materials and forwards its recommendations and materials to the Secretary (or designee).

10) The Secretary (or designee) approves or disapproves the request for HHS to support the research.

11) OHRP notifies the referring institution in writing of the Secretary's (or designee's) decision.

12) At the Secretary's (or designee's) discretion, the HHS decision, detailed rationale for the decision, and supporting materials are posted on the OHRP website.

13) If the Secretary (or designee) approves the proposed research with stipulations, the investigator must modify the research proposal and submit it to the local referring IRB for review and approval.

14) The IRB submits the approved revised protocol to OHRP for final concurrence.

Appendix C

OHRP Procedures for a 407 Panel Process for Multi-Site Research

1) The funding agency and the principal investigator of the study should be informed of OHRPs receipt of a request for review under the 407 process. Any decision on the part of the sponsor or the principal investigator to eliminate a study site should not influence the 407 process.

2) OHRP may seek information from other study sites to determine whether the 407 designation is appropriate. However, if after feedback the IRB requests review under the 407 process, OHRP should determine whether it is appropriate to proceed.

3) OHRP should determine whether, pending completion of the 407 process, suspension or termination of enrollment at other sites may be harmful to currently enrolled participants or to the gathering of information vital to the welfare of children.

4) Whether enrollment has or has not begun, when OHRP determines that review under the 407 process should commence, it may be appropriate to postpone enrollments if the IRB requesting review under the 407 process has raised concerns that:
    a) A study judged by other IRBs to have no prospect for direct benefit poses more than a minor increment over minimal risk; *or*
    b) A study judged by other IRBs as approvable under HHS regulations at 45 CFR 46.405, does not in fact offer a prospect of direct benefit.

   The final decision to suspend or terminate enrollment in a study should rest with OHRP, not the agency supporting the research.

5) If OHRP has determined that enrollment at other sites should be suspended or terminated, OHRP should first attempt to convince the IRBs, the investigators, and the supporting agencies to voluntarily suspend enrollment pending the completion of the 407 process. If the IRBs, Principal Investigators, and/or the funding agency nevertheless refuse to suspend or terminate enrollment, despite consultation with OHRP, OHRP should exercise its appropriate legal authority to effectuate the suspension or termination of enrollment.

6) Regardless of whether or not enrollment is stopped, OHRP should make determinations regarding the provision of additional information to the parents or guardians of already enrolled subjects. The IRBs should decide the process by which that information will be conveyed to the parents or guardians.

7) When OHRP determines that enrollment should be suspended pending completion of the 407 process, each IRB should determine the most appropriate way to communicate this information to parents or guardians whose children are study participants.

8) When OHRP determines that enrollment should *not* be suspended pending completion of the 407 process, parents or guardians should be informed if it is reasonable to assume that knowledge that a review is being conducted would raise legitimate parental or guardian

concerns about withdrawing participation in light of a recalculation of risk and prospective benefits. For example:

a) A protocol approved under HHS regulations at 45CFR6.405 may *not* provide direct benefit; or
b) A protocol approved under HHS regulations at 45CFR46.406 may present more than minor increment over minimal risk.

9) If enrollment is permitted to continue, but *the Secretary has determined* that the risk-benefit calculus has significantly changed as a result of a 407 review, re-consent should be required for continued subject participation.

10) If *the Secretary rules that the study should be disapproved,* but *previously enrolled* participants are permitted to continue until being transitioned off the study, parents or guardians of the subjects should be informed that new enrollments have stopped *and their re-consent for the period which the child remains on the study should be obtained.*

11) If a child has completed participation in a study, it may be necessary to notify the child's parents or guardians. This determination should be based on whether the review under the 407 process has produced new information pertinent to the continued welfare of the child.