

NEW DAIDS REQUIREMENTS FOR PROTOCOL REGISTRATION

Required Documentation of Pediatric
Risk/Benefit Category

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November 30, 2005



Today's goals

- To provide information with respect to DAIDS requirements for the documentation of Pediatric Risk/Benefit.
- To provide sites with additional information for successful protocol registration.

Overview
Office for Human Research
Protections (OHRP)
45 CFR 46 Subpart D



45 CFR 46 Subpart D

- Provides additional protections for children involved as subjects in research
- This regulation has been in place since 1983.

45 CFR 46 Subpart D

§46.401 To what do these regulations apply?

To all research involving children conducted or supported by DHHS, both in the United States and internationally.

§46.402 Definitions

“Children” are 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.

45 CFR 46 Subpart D

IRB Duties: To determine the pediatric risk for each protocol as applies to the following categories

§46.404 Research not involving greater than minimal risk

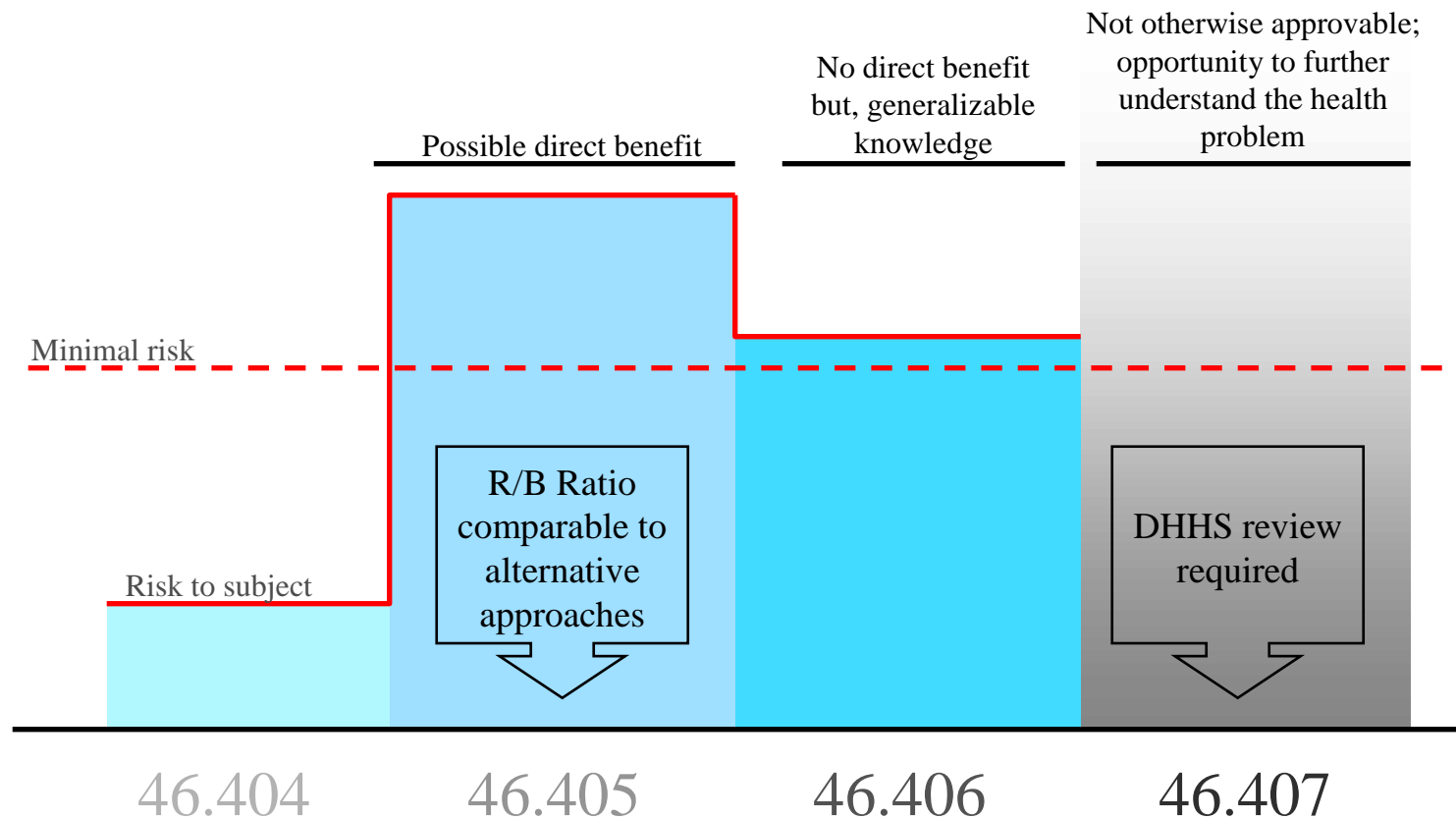
§46.405 Research involving greater than minimal risk but presenting the prospects of direct benefit to the individual subjects

45 CFR 46 Subpart D

§46.406 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

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children


Pediatric risk/benefit categories



DAI DS Protocol
Registration Requirements
for Documentation of
Pediatric Risks



July 8, 2005 letter from DAIDS Office for Policy and Clinical Research Operations (OPCRO)

 <p>DEPARTMENT OF HEALTH & HUMAN SERVICES</p>	<p>Public Health Service</p> <hr/> <p>Division of AIDS National Institutes of Health National Institute of Allergy and Infectious Diseases</p>	<p>Principal Investigators and Study Coordinators, Network Leadership, and Operations Offices July 8, 2005 Page 2</p>						
<p>To: Principal Sites, Network</p> <p>Date: July 8, 2005</p> <p>Subject: Required for inclusion in the 45 CFR 46.404-407* category</p>	<p>For research projects including children or adolescents, the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID) requires documentation of the IRB/EC designation of a risk/benefit category from 45 CFR 46.404-407* and IRB/EC approval for involvement of children based on the determinations specified in that category. The documentation may be in the IRB/EC approval letter or in other official correspondence from the IRB/EC to the investigator.</p>							
<p>As you know, Institutional Review Boards (IRBs) have certain responsibilities to research subjects. The Department of Health and Human Services (DHHS) is currently reviewing the IRB/EC approval process for research involving children and adolescents to ensure that the process is satisfying the conditions stated in U.S. Code of Federal Regulations (CFR) Title 45 Part 46, Subpart D: "Additional DHHS Protections for Children Involved as Subjects in Research."</p>	<p>Richard Hafner, MD Acting Director Office for Policy and Clinical Research Operations</p>							
<p>For research projects including children or adolescents, the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID) requires documentation of the IRB/EC designation of a risk/benefit category from 45 CFR 46.404-407* and IRB/EC approval for involvement of children based on the determinations specified in that category. The documentation may be in the IRB/EC approval letter or in other official correspondence from the IRB/EC to the investigator.</p> <p>This documentation will be required to complete DAIDS protocol registration for all clinical studies enrolling children or adolescents that are reviewed by an IRB/EC after July 24, 2005. This requirement applies to the initial and annual IRB/EC reviews of research protocols and to any subsequent reviews of amendments or Letters of Amendment involving potential study risks or benefits. Protocol registration will not be approved if this documentation is not received.</p>	<p>This documentation will be required to complete DAIDS protocol registration for all clinical studies enrolling children or adolescents that are reviewed by an IRB/EC after July 24, 2005. This requirement applies to the initial and annual IRB/EC reviews of research protocols and to any subsequent reviews of amendments or Letters of Amendment involving potential study risks or benefits. Protocol registration will not be approved if this documentation is not received.</p>							
<p>*As per CFR 45 Part 46.404-407, research involving children or adolescents as subjects. For the criteria to make a determination regarding the waiver of parental permission for adolescent participation when applicable.</p>	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">45 CFR §46.404</td> <td>Research not involving greater than minimal risk.</td> </tr> <tr> <td>45 CFR §46.405</td> <td>Research involving greater than minimal risk but presenting the prospects of direct benefit to the individual subjects.</td> </tr> <tr> <td>45 CFR §46.406</td> <td>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.</td> </tr> </table>		45 CFR §46.404	Research not involving greater than minimal risk.	45 CFR §46.405	Research involving greater than minimal risk but presenting the prospects of direct benefit to the individual subjects.	45 CFR §46.406	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.
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45 CFR §46.406	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.							

Protocols currently affected

Network	Study Number	Full Title
AACTG	A5030	A Phase III, Prospective, Randomized, Double-Blind Trial of Valganciclovir Pre-Emptive Therapy for Cytomegalovirus (CMV) Viremia as Detected by Plasma CMV DNA PCR Assay
AACTG	A5068	A Randomized Phase I/II Study of Intermittent Withdrawal of Antiretroviral Therapy as an Immunization Strategy and Double-Blinded Immunization with ALVAC-HIV vCP1452 in Subjects with Persistent CD4+ Cell Counts Greater than 400 cells/mm ³ & Undetectable PI
AACTG	A5073	A Randomized Phase II Open Label Study to Compare Twice Daily Potent Antiretroviral Therapy With Once Daily Potent Antiretroviral Therapy and to Compare Self-Administered Therapy and Therapy Administered Under Direct Observation
AACTG	A5126	A Phase II Study of the Predictive Value of Pharmacokinetic-Adjusted Phenotypic Susceptibility (C12h/IC ₅₀) on Antiretroviral Response to Ritonavir-Enhanced Protease Inhibitors in Subjects with Failure of Previous Protease Inhibitor-Based Regimens
AACTG	A5142	A Phase III, Randomized, Open-Label Comparison Of Lopinavir/Ritonavir Plus Efavirenz Versus Lopinavir/Ritonavir Plus 2 NRTIs Versus Efavirenz Plus 2 NRTIs As Initial Therapy For HIV-1 Infection
AACTG	A5157	An Open-Label, Dose-Escalation Pilot Study Of Acetyl-L-Carnitine For The Treatment Of Dideoxynucleoside-Associated Distal Symmetric Peripheral Neuropathy
AACTG	A5202	A Phase IIIB, Randomized, Trial of Open-Label Efavirenz or Atazanavir with Ritonavir in Combination with Double-Blind Comparison of Emtricitabine/Tenofovir or Abacavir/Lamivudine in Antiretroviral-Naive Subjects
AACTG	A5224S	Long-Term Metabolic Assessments in Subjects Treated with Emtricitabine/Tenofovir or Abacavir/Lamivudine with either Efavirenz or Atazanavir with Ritonavir
AACTG	A5207	A Phase II Randomized Comparison of Three Antiretroviral Strategies Administered for 7 or 21 Days to Reduce the Emergence of Nevirapine Resistant HIV-1 Following a Single Intrapartum Dose of Nevirapine.
AACTG	A5221	A Strategy Study of Immediate Versus Deferred Initiation of Antiretroviral Therapy for HIV-Infected Persons Treated for Tuberculosis with CD4<200 Cells/mm ³
AACTG	ACTG 362	Long Term Assessment for Metabolic, Cardiovascular and Neurologic Complications in Subjects With Past CD4 Cells/mm ³ < 50 Who Increased CD4 Cells/mm ³ to >100 on HAART.
AACTG	ACTG 371	A Phase Trial to Evaluate the Safety and Efficacy of Induction Treatment with Lamivudine plus Stavudine plus Abacavir plus Amprenavir/Ritonavir Followed by Supervised Treatment Interruption in Subjects with Acute HIV Infection or Recent Seroconversion
AIEDRP	CORE01	AIEDRP CORE01- A5228 Database Protocol

Examples of IRB documentation of risk

SEP-20-2005 16:21 [REDACTED] P. 07/33

CHR APPROVAL LETTER

TO: [REDACTED]

RE: P1055, Version 1.0: Psychiatric Co-Morbidity In Perinatally HIV- Infected Children And Adolescents

The Committee on Human Research (CHR) has reviewed and approved this application to involve humans as research subjects. This included a review of all documents attached to the original copy of this letter.

Specifically, the review included but was not limited to the following documents:
Subject/Parent Consent Form for Subjects 13 years and older, Dated 9/09/05
Parental Consent Form for Subjects 12 years old and younger, Dated 9/09/05
Multicenter Protocol Version 1.0, Dated 12/10/04
Assent Form for Children Ages 7-12, Dated 9/09/05

Comment: The CHR determined that enrolling minors in this study is acceptable under the provision of federal regulations (45 CFR 46.404). The research involves minimal risk. Parental permission will be obtained, as will the assent of the minors. As the study was approved under 45 CFR 46.404, wards of the state may be enrolled with permission of their legal guardian. Please make your intent to enroll wards explicit in all future submissions.

APPROVAL DATE: September 19, 2005 EXPIRATION DATE: September 19, 2006 Full Committee Review

GENERAL CONDITIONS OF APPROVAL: Please refer to www.research.usf.edu/chr/Apply/chrApprovalCond.asp for a description of the general conditions of CHR approval. In particular, the study must be renewed by the expiration date if work is to continue. Also, prior CHR approval is required before implementing any changes in the consent documents or any changes in the protocol unless those changes are required urgently for the safety of the subjects.

HIPAA "Privacy Rule" (45CFR164): This study requires individual consent/authorization for use and/or disclosure of Protected Health Information (PHI).

Sincerely,
[REDACTED]

Examples of IRB documentation of risk

Sep-21-2005 03:22pm From- [REDACTED] T-931 P.004/027 F-688

[REDACTED]

Date: September 19, 2005
 Protocol Number: 0400103
 Principal Investigator: [REDACTED]
 Department / Division: [REDACTED]
 Sponsor:

Title: *PACTG P1025, Version 2.0, dated 7/10/2002, entitled, "Perinatal Core Protocol,"*

Thank you for your response to requests from a prior review of your application listed above. This type of response qualifies for expedite review under FDA and OHRP regulations. This is to confirm that your application is now fully approved.

This action involves:

- New proposal/project
- Waiver of Consents
- Continuing Review of Previously Approved Protocol
- Protocol Amendment
- Revised Informed Consent Form
- Adverse Events / Serious Adverse Events
- Other:
- Receipt of _____

The following documents were reviewed under this submission:

- Informed Consent Document English and Spanish
- Assent Document English and Spanish
- Protocol
- Survey Instrument
- Package Insert
- Advertisement
- Investigator Brochure
- FDA #1572
- Others: Investigator Record

In compliance with federal regulations the approval of this project is valid through for a period of one year or less from the time of the most recent IRB review. Approval for this study is valid

[REDACTED]

[REDACTED] From- [REDACTED] T-931 P.005/027 F-688

Page 2 of 2

through August 23, 2006. The most recent protocol version is: N/A. The most recent consent

For protocols/ research projects including children or adolescents please indicate the risk/ benefit category as determined by the IRB:

- 45 CFR §46.404 Research not involving greater than minimal risk.
- 45 CFR §46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
- 45 CFR §46.406 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.
- 45 CFR §46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

[REDACTED]

mco

Examples of IRB documentation of risk

DATE: 1/18/2005
FROM: Chair, [REDACTED]-IRB
SUBJECT: Minutes of the [REDACTED]-IRB Meeting Held on [REDACTED]
TO: Members, [REDACTED]-IRB
Through: Clinical Director, [REDACTED]

Minutes of the [REDACTED] IRB Meeting Held on Monday, January 14, 2005

MEMBERS PRESENT:

Dr. [REDACTED], Chair	HIV
Dr. [REDACTED], Vice Chair	Biostatistician
Ms. [REDACTED]	Community Representative/Non-Scientist
Dr. Ivan Russ	Immunology/Basic Science
Dr. [REDACTED]	Internal Medicine/Infectious Diseases/Pediatrics
Rabbi [REDACTED]	Non-Scientist/Religious
Ms. [REDACTED]	Nurse

MEMBERS ABSENT:

Dr. [REDACTED]	Pharmacology
Dr. [REDACTED]	Ethics

ALTERNATE MEMBERS PRESENT:

None

The meeting convened at 12:15 p.m. with a quorum present (6 plus the Chair).
The Chair announced the following conflict of interest:

- Dr. [REDACTED], Continuing Review for Protocol [REDACTED]

CONTINUING REVIEWS

I. Continuing Review

PROTOCOL NO.: [REDACTED]

TITLE: Diagnosis and Treatment of Leishmanial Infections

PRINCIPAL INVESTIGATOR: [REDACTED], MD.

ASSOCIATE INVESTIGATOR(S): [REDACTED], MD; [REDACTED], MD; [REDACTED], Ph.D.

EXPIRATION DATE: 2/14/2005

HSP TRACKING NO.: 145

PROTOCOL DESCRIPTION: To study the natural history of leishmanial infections and to provide an opportunity for the [REDACTED] medical staff to learn about this relatively unusual parasitic infection and to have some experience in treatment of leishmaniasis.

a) Discussion:

The investigator requests renewal with new subject accrual to continue. Three new subjects have been enrolled since the last review, for a total of 16 accrued since the protocol began. (Ceiling set by the IRB is 75.) Existing radiation is used as medically indicated. An IND is held by [REDACTED].

No new information has appeared in the literature that would affect risk or benefit to human subjects. No unexpected events have occurred. This research has led to the publication of an article in *Clinical Topics in Infectious Diseases*.

[REDACTED] IRB Minutes

In the consent, there is no mention of possible side effects of having a PICC line placed. Although patients would have to have a PICC line for alternative therapy (amphotericin), the risks should be delineated.

There were no controverted issues.

b) Stipulations:

d) IRB Decision and Vote:

The IRB motioned and seconded the recommendation that this Continuing Review be Approved for 12 months with stipulations to the Chair. Motion passed unanimously (Total = 6; Vote: For = 6, Opposed = 0, Abstained = 1).

Risk Level: 3. The research involves more than a minor increase over minimal risk to subjects (45 CFR 46.102(h)(i)). This amendment does not alter the expected risks.

Children's Risk Category: 2. Research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects (45 CFR 46.405).

Benefit: 2. The research involves the prospect of direct benefit (45 CFR 46.102(h)(i)). This amendment does not alter the expected benefits.

Examples of IRB documentation of risk

It is also acceptable to include the category description without the corresponding number:

“The Board determined that this study involves greater than minimal risk but presents the prospects of direct benefit to the individual subjects. You may now begin the proposed research.”

This description corresponds to §46.405

Summary

Acceptable documents

- IRB approval letter
- IRB minutes
- IRB memo

Acceptable formats

- Only category number
- Only category description
- Category number and description

Special cases



Exclusion of Minors

- What if the site will not enroll subjects under the legal age of consent?
- Site provides the Protocol Registration Office (PRO) with a memo from the Investigator of Record (IoR) documenting this.

Example: Exclusion of Minors

To: Daniel Molina, Protocol Registration Manager
Regulatory Compliance Center
Technical Resources International

From: [REDACTED]

Prepared By: [REDACTED]

Date: September 19, 2005

RE: **CPCRA 065G, Version 1.0 (2/08/2005): "Anal Dysplasia: A Sub-study of A Large, Simple Trial Comparing Two Strategies for Management of Anti-Retroviral Therapy (SMART)"**

Memo to Sponsor

This memo to the study sponsor and the Technical Resources International (TRI) Regulatory Compliance Center is to acknowledge that as per 45 CFR 46.404-407, the Research & Education Group has not, and will not in the future, enroll subjects younger than eighteen years of age into any CPCRA protocol conducted at our sites 003, 004, 005, 007, 010, 011, 012, 017, 019, 021, and 023.

Please let me know if there is any additional information that you require. Thank you for your continued assistance.

Additional Informed Consents

Additional Languages:

- What if a site received approval from the IRB and PRO for the current version of the protocol before July 24, 2005 and later submits an additional language informed consent (IC)?
- If the original IRB document(s) contained the pediatric risk determination, then it is not required for additional language ICs.

Additional Informed Consents

Additional ICs (i.e. stored specimens, pregnancy etc.):

- What if a site received approval from the IRB and PRO for the current version of the protocol before July 24, 2005, and later submits an additional IC for the storage of specimens?
- The documentation of pediatric risk is protocol and version specific and is not required for each type of IC submitted.

Protocol Amendments

- Does the determination of pediatric risk apply to Protocol Amendments?
- Yes

Protocol Amendments

- What if the IRB Amendment Approval letter does not include the Pediatric Risk Category?
- Send the PRO a copy of the original IRB letter which included the Pediatric Risk Category. **Plus**, provide a memo from the IRB stating that the Amendment did not affect the pediatric risk category.
- If the pediatric risk was never documented, then the Amendment approval needs to include this determination

Age of consent is not 18 years old

- What if the legal age of consent where the site is located is greater than 18 years old?
- Each IRB should determine when 45 CFR 46 Subpart D is applicable. If the legal age of consent is greater than 18 years old, the pediatric risk documentation requirement may also apply to adult studies.

Age of consent is not 18 years old

- What if the legal age of consent where the site is located is less than 18 years old?
- If the IRB decides that the pediatric risk determination is not applicable, then the site must provide the PRO with justification from the IRB stating the local legal age of consent.

Emancipated Minors

- What about studies involving emancipated minors?
- In some locations, minors who are pregnant may be considered adults for the purpose of consent.
- If a protocol is specific to this population, the site should provide IRB justification as to why a pediatric risk determination has not been made.
- This documentation may include local laws regarding this population.

Multiple IRB Reviews

- What if more than one IRB is required to review a protocol for implementation at a site? (i.e. domestic and international IRBs)
- Each reviewing IRB must provide documentation of their pediatric risk determination, unless one has entered into an IRB authorization agreement to serve as the IRB of record for the other IRB(s).
- The IRB of record should demonstrate knowledge of local context.

Additional Protocol Registration Guidance



Site IC disapproval

Most common reason for IC disapproval:

Basic Element 6: Research related injury

- If the site or other affiliated parties are specifically mentioned in the IC as not providing compensation, NIH must also be specified in the IC.
- The IC should not contain vague language (i.e. "...the site may or may not provide...").

Missing Identifiers

- Missing identifiers may result in a delay in protocol registration review.
- DAIDS-required identifiers:
 - Protocol Title
 - Protocol Number
 - Protocol Version Number
- Documents that require identifiers: IRB letters, all ICs, memos from IRB, memos from site, etc.

Thank You!

E-mail: protocol@tech-res.com

Phone: 1-301-897-1707

Fax: 1-800-418-3544 or 1-301-897-1701

<http://rcc.tech-res-intl.com>

