



**Society for Clinical Trials 32<sup>nd</sup> Annual Meeting**

**Workshop P5  
Trial and Site Management for  
Multi-Center Trials**

**Part 3 of 3**

**Sunday, May 15, 2011**

**8:00 AM - 12:00 PM**

**Georgia B**



# **Workshop - Trial and Site Management for Multi-Center Trials**

## Extra documents

1. Paperwork needed for NIH funded studies
2. Sample Publication Policy – US site
3. Sample Publication Policy – UK site
4. Example Co-sponsorship Agreement
5. Sample Agreement for US Central Office and non-US site

# Specific Paperwork for NIH funded studies

Each participating site requires the following:

## **1. Assurance of compliance with United States Federal regulations for protection of human subjects in research:**

Your institution must assure that it will comply with the Common rule (for NIH, 45 CFR 46.103; for FDA 21CFR subpart 50, HIPPA).

In many cases your institution will have many NIH projects underway and will have received a Federal-Wide Assurance (FWA) number. Once an institution has this number your project is automatically covered. You will just need to provide the number to the DCC.

If yours is the first NIH project to be undertaken at your institution the DCC can cover you under their FWA. You will have to sign a special agreement for this to happen. But if your institution is collaborating on multiple NIH studies it must apply for its own FWA number. Here is a web link that has instructions about this. (<http://ohrp.cit.nih.gov/efile/FwaStart.aspx>)

## **2. Documentation of education on the protection of human subjects in research**

The collaborator at your site and all other research personnel must provide this documentation of education. Your institution will stipulate what this education needs to be. It is often some sort of on-line course that can be completed at your own pace.

Some examples are:

Protection of Human Research Subjects: Computer-Based Training for Researchers - <http://phrp.nihtraining.com/users/login.php> This is an NIH-sponsored course.

Interagency Panel on Research Ethics - <http://www.pre.ethics.gc.ca/english/tutorial>. This is a Canadian course that covers the Canadian regulations.

## **3. Contracts/Consortium Agreements**

The DDC must arrange contracts/consortium agreements with all participating clinical sites. These contracts have wording and specific clauses required by NIH. The DCC is accountable to the NIH for the overall performance of the project, appropriate expenditure of the grant funds by all parties, and all other NIH requirements. The contracts outline for the sites their responsibilities. Often these are standard contracts but negotiation on some things can be undertaken.

## **4. Identification numbers required for anyone dealing with the US Federal Government.**

These are:

DUNS number (Data Universal Number System)

EIN number (Employer Identification Number)

CCR (Central Contractor Registration)

NATO Commercial and Governmental Entity (NCAGE) Code (required for foreign sites only)

Your site may have some, or all, of these numbers already. You can search at [https://www.bpn.gov/bincs/begin\\_search.asp](https://www.bpn.gov/bincs/begin_search.asp) for existing DUNS and CAGE numbers. If your site has received NIH funds at any time in the past they will have an EIN number.

If you need to get any of these four numbers the following website will take you through the process - [http://era.nih.gov/ElectronicReceipt/preparing\\_grantsgov\\_reg.htm](http://era.nih.gov/ElectronicReceipt/preparing_grantsgov_reg.htm)

#### **5. Bayh-Dole Acknowledgement**

This is a form that all trial employees need to sign regarding the process to be followed for any inventions arising from federally supported research.

## ***SAMPLE POLICY FROM US SITE***

***[STUDY NAME]***

### **Publication and Presentation Policy**

#### **A. GOALS**

1. To encourage high quality publications and presentations in a timely fashion.
2. To encourage broad participation by *[STUDY]* investigators in publications and presentations.
3. To encourage multidisciplinary and creative use of the *[STUDY]* data and resources.
4. Ensure appropriate recognition of *[STUDY]* investigators.

#### **B. SCOPE OF THE GUIDELINES**

The policy covers papers, abstracts, and presentations that involve unpublished data collected as a part of the *[STUDY]* study. These policies will remain in force for the duration of data analysis by the *[STUDY]* Executive Committee.

#### **C. *[STUDY]* PUBLICATION REVIEW**

The Executive Committee will have overall responsibility for publications from *[STUDY]*.

#### **D. TYPES OF REPORTS**

These guidelines deal with 4 different types of reports.

- Main papers: Primary hypotheses and outcomes to be presented and published by whole *[STUDY]* Study Group
- Other study publications: May be undertaken by smaller groups for the *[STUDY]* Study Group with all participants at the end of the paper.
- Abstracts submitted to national or international meetings.
- Presentations made to national or international meetings.

#### **E. AUTHORSHIP AND ACKNOWLEDGEMENTS**

- Authors must participate in the writing of the paper in accordance with the International Committee of Medical Journal Editors guidelines (N Engl J Med 1991; 324:424-8). First authors are expected to delete names from the final list of authors if those individuals have not participated in the writing and/or analysis of the paper in accordance with those guidelines.
- All *[STUDY]* papers and abstracts should include either “[*STUDY*] Investigators” or “for the *[STUDY]* Study Group” in the authorship line.

- All *[STUDY]* papers should include an "Acknowledgements" section that lists the *[STUDY]* investigators and principle staff at the Coordinating Center, Statistical and Data Management Center, Imaging Center, and Clinical Sites. Also the NIH NINDS grant number should be cited (*[Grant Number]*).

When the results from the genome scan are cited, acknowledge CIDR as: "Genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institute of Health, to Johns Hopkins University, contract #*[contract number]*."

- Authorship of main papers: Authorship of main papers may include investigators from the Coordinating Center, the Statistical and Data Management Center, Imaging Center, clinical sites, and NINDS Study Representative. In general, these authors should be those who have made the most substantial contribution to the study. The Executive Committee will recommend the composition of authorship for the main papers and may make exceptions to these guidelines.
- Authorship of other papers: Where feasible and appropriate, at least one investigator from the Coordinating Center or Data Management Center will work the investigator proposing the analysis and publication in completion of the analysis and manuscript using *[STUDY]* data.

#### First authorship of *[STUDY]* papers

- First authors of main papers will be *[STUDY]* Study Investigators/Group. For other *[STUDY]* papers and abstracts, *[STUDY]* Investigators will also receive priority.
- In general, the investigator who first conceived of the project and submitted a plan for the manuscript to the Executive Committee should have the option of serving as first author, so long as they complete the paper within a reasonable amount of time.

#### 1. Co-authorship

- The order of authorship on a paper should be proposed by the writing group to the *[STUDY]* Executive Committee for that project. In general, the authors will appear in order of contribution to the writing and analysis of the paper.
- When contributions to writing and analysis have been similar, priority should be given, in order of preference, to 1) *[STUDY]* investigators or staff 2) more junior authors, 3) those who have contributed to a greater degree to management and data collection for the study, and 4) *[STUDY]* investigators or staff who have had fewer opportunities to author *[STUDY]* papers.

## 2. Disclosures

- *[STUDY]* papers should include a paragraph describing the source of funding (NIH/NINDS and CIDR) and their role in the analysis, writing and review of the paper.
- NIH funding (grant # *[Grant Number]*) should also be acknowledged.

## F. ANALYSIS OF DATA

- The Statistical and Coordinating Center will finalize study-wide data and will perform analysis to support specific proposals upon priority and approval established by the Executive Committee.
- Analyses for the main papers will be performed collaboratively by the Statistical and Coordinating Center. Analyses done by other groups must be first approved by the Executive Committee.

## G. ASSIGNMENT AND APPROVAL PROCESS FOR ANALYSIS PROPOSALS

### 1. Analysis plans

- The first step for all *[STUDY]* papers, abstracts, posters, and presentations of unpublished data is for an investigator to submit a plan to the Executive Committee. The plan should specify the content including the hypothesis, patient population (inclusion, exclusion), and data analysis and tables.
- The proposed journal or meeting and deadlines need to be specified.
- Priority will be determined by *[STUDY]* Executive Committee and *[STUDY]* Statistical and Coordinating Center.
- Status communicated to investigator/working group.

### 2. Timeline

If the authors have not made substantial progress (as defined by the *[STUDY]* Executive Committee) on the analysis within 6 months or the Publications Committee has not received an abstract, presentation, or manuscript within one year after approval of the analysis plan, the Executive Committee will review the progress on that plan and may offer first authorship to others in the writing group. An exception will be when final data are not available. In that case, the first author will have one year from the time that the data first became available or approval date, whichever is later.

## I. [STUDY] PAPERS

- Prior to preparation of the manuscript, send to [STUDY] Executive Committee the title, abstract, authors, proposed journal.
- Authors are to be proposed by working groups.
- All participants will be listed as co-authors ([STUDY] Study Group).
- The manuscript will be reviewed by [STUDY] Executive Committee before submission to verify accuracy of the data.

## J. [STUDY] ABSTRACTS, POSTERS AND PRESENTATIONS

- Abstracts, posters and/or presentations will be of outcome (1<sup>o</sup> or 2<sup>o</sup> hypotheses) by the entire study group.
- All abstracts posters and presentations must be based on an approved analysis plan.
- Deadlines: Authors who plan to submit an abstract must notify the Coordinating Center 3 weeks in advance of the abstract deadline. Drafts of abstracts and posters and outlines of presentations including the data and conclusions must be received by the Coordinating Center at least 10 working days before the abstract deadline or date of presentation. Executive Committee reviewers must indicate their approval or disapproval and suggested revisions within 5 working days from the fax date of the abstract or presentation. A committee member may withhold approval pending revision. In such cases, authors must respond to the comments of the committee member. For abstracts, approval of at least 2 of the reviewers, with no reviewers disapproving, is required. Failure to respond to request for approval within the time limit will be taken as abstention. Authors and presenters will be notified about approval and recommended changes within 5 working days of the mailing or fax date. Send to [STUDY] Executive Committee the title, presenter, audience, and data content.
- For national or regional meetings the authors need to send to [STUDY] Executive Committee for review the abstract, authors, meeting, deadline date, and presentation date for final review of accuracy.

Request for use of data from the *[STUDY]* database

|   |  |
|---|--|
| Date of Request                                   |  |
| Investigator Name                                 |  |
| Investigator Address                              |  |
| Investigator email:                               |  |
| Investigator Direct Line:                         |  |
| Description of proposed Presentation/Manuscript:  |  |
| Data elements needed for Presentation/manuscript: |  |

All publications/presentations must acknowledge:

This study was supported in part by the National Institute of Neurological Disorders and Stroke of the National Institute of Health grant number *[Grant Number]*.

Any publications/presentation using genetic results must acknowledge:

Genotyping services were provided by the Center for Inherited Disease Research (CIDR).

CIDR is fully funded through a federal contract from the National Institutes of Health to the Johns Hopkins University, Contract Number *[Grant Number]*.

# PUBLICATION POLICY - UK EXAMPLE

## PUBLICATION POLICY FOR XXXXXX Study AUTHORSHIP POLICY

### 1. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals (see references) and are in accordance with the rules of the International Committee of Medical Journal Editors.

#### a. Group authorship

Group authorship will be appropriate for some publications, such as main reports. This will apply when the intellectual work underpinning a publication 'has been carried out by a group, and no one person can be identified as having substantially greater responsibility for its contents than others'.<sup>1</sup> In such cases the authorship will be presented by the collective title - The XXXXXX Trial Group - and the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. In some situations one or more authors may take responsibility for drafting the paper but all group members qualify as members; in this case, this should be recognised using the byline 'Jane Doe *and* the Trial Group'.<sup>2</sup> Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the byline would read 'Jane Doe *for* the Trial Group').<sup>2</sup>

#### b. Individual authorship

Other papers, such as describing satellite studies, will have individual authorship. In order to qualify for authorship an individual must fulfil the following criteria<sup>1</sup>:

- i. Each author should have participated sufficiently in the work represented by the article to take public responsibility for the content.
- ii. Participation must include three steps:
  - conception or design of the work represented by the article OR analysis and interpretation of the data OR both; AND
  - drafting the article or revising it for critically important content; AND
  - final approval of the version to be published.

Participation solely in the collection of data is insufficient by itself and those persons who have contributed intellectually to the article but those contributors do not justify authorship may be acknowledged and their contribution described.<sup>1</sup>

#### c. Determining authorship

Tentative decisions on authorship should be made as soon as possible.<sup>1</sup> These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Steering Committee.

## 2. AUTHORSHIP FOR PUBLICATION ARISING FROM XXXXXX

### a. Operationalising authorship rules

We envisage two types of report (including conference presentations) arising from the XXXXXX trial and its associated projects:

- i. *Reports of work arising from the main XXXXXX trial* - If all grant-holders and research staff fulfil authorship rules, group authorship should be used under the collective title of 'The XXXXXX Trial Group'; if one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to 'Jane Doe and the XXXXXX Trial Group'.
- ii. *Reports of satellite studies and subsidiary projects* - Authorship should be guided by the authorship rules outlined in Section 1 above. Grant-holders and research staff not directly associated with the specific project should only be included as authors if they fulfil the authorship rules. Grant-holders and research staff who have made a contribution to the project but do not fulfil authorship rules should be recognised in the Acknowledgement section. The role of the XXXXXX Trial Group in the development and support of the project should be recognised in the Acknowledgement section. The lead researcher should be responsible for ratifying authorship with the Project Management Group.

For reports which specifically arise from the XXXXXX trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to 'Jane Doe for the XXXXXX Trial Group'. If individual members of the group are dissatisfied by a decision, they can appeal to the Management Group for reconciliation. If this cannot be achieved, the matter should be referred to the Steering Group.

### b. Quality assurance

Ensuring quality assurance is essential to the good name of the trial group. For reports of individual projects, internal peer review among members of the Project Management Group is a requirement prior to submission of papers. All reports of work arising from the XXXXXX trial including conference abstracts should be peer reviewed by the Project Management Group.

The internal peer review for reports of work arising from the XXXXXX project is mandatory and submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. The Project Management Group will be responsible for decisions about submission following internal peer review. If individual members of the group are dissatisfied by decisions, the matter may be referred to the Steering Group.

The Project Management Group undertake to respond to submission of articles for peer review at the Project Management Group Meeting following submission (assuming the report is submitted to the trial secretariat in Aberdeen at least two weeks prior to the meeting).

## REFERENCES

1. Huth EJ (1986). Guidelines on authorship of medical papers. *Annals of Internal Medicine*, **104**, 269-274.
2. Glass RM (1992). New information for authors and readers. Group authorship, acknowledgements and rejected manuscripts. *Journal of the American Medical Association*, **268**, 99.

# Example Co-sponsorship Agreement

## Allocation of Co-sponsorship Responsibilities for the ??? Trial

**Between:**

??? (Central Office location)

**and**

?? (site)

**and**

??? (Site Collaborator)

**All responsibilities allocated ✓, must be initialed to indicate acceptance**

| Responsibilities   | Central Office | Site | Collaborator |
|--|----------------|------|--------------|
| 1. Assess the quality of the research  | ✓              | ✓    |              |
| 2. Assess the quality of the research environment premises <sup>1</sup>  | ✓              | ✓    |              |
| 3. Ensure appropriate experience of the site Collaborator(s) <sup>2</sup>  | ✓              | ✓    |              |
| 4. Ensure arrangements, systems and resources will allow the collection of high quality, accurate data and the appropriate data analysis and data protection | ✓              | ✓    |              |
| 5. Ensure that arrangements are in place for the research team to access resources and support to completely deliver the research                            | ✓              | ✓    | ✓            |
| 6. Ensure that arrangements are in place to review significant developments  | ✓              |      |              |
| 7. Ensure arrangements are in place to monitor the research for compliance or agree with another organisation to provide the facility                        | ✓              |      |              |
| 8. Ensure provision has been made for insurance or indemnity   | ✓              | ✓    |              |
| 9. Ensure the research proposal respects the dignity, rights, safety and well-being of participants and the relationship with care professionals             | ✓              | ✓    |              |

| Responsibilities   | Central Office |  | Site |  | Collaborator |  |
|--|----------------|--|------|--|--------------|--|
|  |                |  |      |  |              |  |
| 10. Ensure that the research proposal is worthwhile, of high scientific quality and represents good value for money                    | ✓              |  | ✓    |  |              |  |
| 11. Ensure that all scientific judgements made in relation to responsibilities set out here are based on independent and expert advice | ✓              |  |      |  |              |  |
| 12. Ensure that appropriate arrangements are in place for the registration of the trial  | ✓              |  |      |  |              |  |
| 13. Ensure that assistance is provided to any enquiry, audit or investigation related to the trial                                     | ✓              |  | ✓    |  | ✓            |  |
| 14. Ensure that arrangements are proposed for disseminating the findings   | ✓              |  | ✓    |  |              |  |
| 15. Ensure adequate financing of the project   | ✓              |  |      |  |              |  |
| 16. Ensure adequate arrangements for the long term storage of Trial Source Data and Patient Health records                             |                |  | ✓    |  | ✓            |  |
| 17. Management of Intellectual Property  | ✓              |  |      |  |              |  |
| 18. Write the protocol   | ✓              |  |      |  |              |  |
| 19. Ensure documented risk assessment of significant hazards associated with the protocol  | ✓              |  |      |  |              |  |
| 20. Ensure appropriate scientific review of the proposed protocol  | ✓              |  |      |  |              |  |
| 21. Ensure statistical advice is sought  | ✓              |  |      |  |              |  |
| 22. Ensure Research Ethics Committee approval obtained before starting   | ✓              |  |      |  | ✓            |  |
| 23. Ensure Trust R&D approval before commencement  |                |  |      |  | ✓            |  |
| 24. Write study specific procedures <sup>3</sup>   | ✓              |  |      |  | ✓            |  |
| 25. Set up and maintain a Trial Master File and essential documentation  | ✓              |  |      |  | ✓            |  |
| 26. Notify protocol amendment(s) to Research Ethics / R&D <sup>4</sup>   |                |  |      |  | ✓            |  |

| Responsibilities  | Central Office |  | Site |  | Collaborator |  |
|---|----------------|--|------|--|--------------|--|
|   |                |  |      |  |              |  |
| 27. Notify early discontinuation of trial to Research Ethics / R&D <sup>4</sup>                               |                |  |      |  | ✓            |  |
| 28. Notify end of trial within 90 days to Research Ethics / R&D <sup>4</sup>                                  |                |  |      |  | ✓            |  |
| 29. Notify R&D of Study Start and End Dates   |                |  |      |  | ✓            |  |
| 30. Take appropriate safety measures in consultation with the other parties                                   | ✓              |  | ✓    |  | ✓            |  |
| 31. Keep auditable records of all adverse events  | ✓              |  |      |  | ✓            |  |
| 32. Ensure that all SAEs are recorded and reported according to local and regulatory requirements             | ✓              |  |      |  | ✓            |  |
| 33. Ensure that Site Collaborators are informed of SAEs   | ✓              |  |      |  |              |  |
| 34. Produce an annual safety report on the research trial and submit to R&D <sup>5</sup>                      |                |  |      |  | ✓            |  |
| 35. Ensuring adequate arrangements for the long term storage of Trial Master File and essential documentation | ✓              |  |      |  | ✓            |  |
| 36. Notify R&D of all study publications annually <sup>6</sup>  |                |  |      |  | ✓            |  |
| 37. Submit annual reports on trial progress to the R&D Office   |                |  |      |  | ✓            |  |

Notes:

1. Quality of premises assessed by Central Office through Centre Survey
2. Experience of Site Collaborators assessed by Central Office through collection of CVs
3. Overall study specific procedures by Central Office; local issues by Site Collaborators
4. Notice of protocol amendments, early discontinuation of trial, and end of trial provided to Site Collaborators by Central Office
5. Safety information provided to Site Collaborators by Central Office: notification of all SAEs, Data Safety Monitoring Board reports (if any), notification of results of other similar trials
6. Trial progress information provided to Site Collaborators by Central Office: monthly recruitment and follow-up tables, monthly newsletter

**DECLARATION OF ACCEPTANCE OF CO-SPONSORSHIP  
ARRANGEMENTS  
for the ??? Trial  
Between:**

??? (Central Office)

**and**

??? (Site)

**and**

??? (Site Collaborator)

In signing this agreement the above parties are confirming that:

- This research trial will be conducted in accordance with the Research Governance Framework for Health & Social Care 2005 The parties confirm that where they have agreed that responsibilities shall be allocated otherwise than in accordance with the Framework this shall not compromise the standards or quality of the research nor the safeguards for those, including the public, who participate in the research.
- Where applicable this research trial will be conducted according to all regulatory requirements of International Conference on Harmonisation GCP/GMP, the UK Competent Authority (MHRA) and Directive/2005/20/EC.
- It is understood that if serious non-compliance, research misconduct and/or fraud are identified through routine or regulatory monitoring the trial will be closed.

I confirm that I have read and agree to accept the responsibilities as detailed and initialled in the Allocation of Co-sponsorship Responsibilities for the ??? Trial

**Signature for (Central Office)**

|            |           |      |
|------------|-----------|------|
| Print name | Signature | Date |
|------------|-----------|------|

**Signature for (Site)**

|            |           |      |
|------------|-----------|------|
| Print name | Signature | Date |
|------------|-----------|------|

**Signature of the Site Collaborator**

|            |           |      |
|------------|-----------|------|
| Print name | Signature | Date |
|------------|-----------|------|

# Sample Agreement for US Central Office and non-US site

## AGREEMENT

This Agreement is by and between [CENTRAL OFFICE], [the site] [which may be part of a bigger organization] for the purpose of support to the [study]. The [STUDY] is funded by the National Institutes of Health/National Institute of Neurological Disorders and Strokes Grant No. ??? attached hereto as Attachment C.

**1. Statement of Work.** On behalf of [SITE], the [?? UNIT] will function as the central point of contact for administrative tasks related to [STUDY] in ????. The [SITE] will act as administrative agent of [CENTRAL OFFICE] by performing specific activities identified in Attachment A.

**2. Period of Performance.** The period of performance under this Agreement shall be from February 1, 2006 through January 31, 2007. Expenditures incurred beyond January 31, 2007 are contingent upon availability of federal funding and will be authorized by written amendment to this Agreement.

**3. Payment Amount.** The estimated payment for [SITE]'s services provided under this Agreement is identified in the budget attached hereto as Attachment B. The annual estimated amount of \$\_\_\_ US Dollars is contingent on availability of funds and will be paid proportional to overall recruitment by nine proposed centers. Such amount shall not be exceeded without written Amendment to this Agreement. In addition and pursuant to Exhibit One, Enrolling Center Template, funding will be provided through [SITE] for payment to Enrolling Centers.

**4. Key Personnel.** Project activities under the [SITE] shall be under the direction of the [SITE] Director, ????. [SITE] shall notify [CENTRAL OFFICE] in writing of any changes of the [SITE] Project Director. Any successor proposed by [SITE] to replace the [SITE] Project Director must have the prior written approval of [CENTRAL OFFICE].

### **5. Fiscal Considerations.**

5.1 Submission of Invoice: [CENTRAL OFFICE] will pay the [SITE] according to payment schedule attached hereto as Attachment B, in arrears, upon submission of an invoice to [CENTRAL OFFICE] at: ????. Such invoices shall be in duplicate (a certified original and one copy) and shall reference the [CENTRAL OFFICE] Agreement Number 122343/122182. Invoice amounts shall be calculated and shown in US Dollars. The basis for such calculation and conversion to US Dollars shall be the Euro value of \_\_\_\_€(as of March 9, 2006 per <http://www.oanda.com/convert/classic>).

5.2 Final Payment: The final payment under this Agreement will be based upon receipt of and acceptance by [CENTRAL OFFICE], all services, information, and/or supplies required herein.

**6. Reporting Requirements.** Reports shall be submitted to [CENTRAL OFFICE] at such time and in such format as the [CENTRAL OFFICE] Project Director and [SITE] Project Director shall agree and as outlined in Attachment A.

**7. Publications.** [??? UNIT] acknowledges that the work to be conducted under this Agreement is part of a multi-center [study] and that an independent joint publication is anticipated to be authored by the investigators in the multi-center [STUDY]. Therefore, [??? UNIT] agrees not to independently publish the any results of the [STUDY] until the multi-center publication has been made.

**8. Termination.** Either party may terminate this Agreement upon thirty (30) days' written notice to the other party. Termination by either party does not relieve the Enrolling Center of the responsibilities of the follow-up phase of the Study as detailed in the Protocol. In the case of termination by [CENTRAL OFFICE], the Enrolling Center will be reimbursed for all non-cancelable commitments under Article 5, Payment Schedule.

**9. Compliance Assurances and Certifications.** [??? UNIT] and [SITE] certify, by signing this document that the following assurances and certifications that apply to the [CENTRAL OFFICE] prime grant are met. Such assurances and certifications required by the [SITE] shall include but are not necessarily limited to:

- a. Human Subjects. Compliance with the requirements of federal policy concerning the safeguarding of the rights and welfare of human subjects who are involved in activities supported by Federal funds.
- b. Patents, Licenses, and Inventions. Compliance with the Standard Patent Rights clauses as specified in 37 Code of Federal Regulations (CFR), Federal Acquisition Regulation (FAR) System or United States Code (U.S.C.) CFR, Part 501, FAR 57.227-11, or U.S.C. 203, whichever is appropriate and applicable.
- c. Non-Delinquency on Federal Debt. AWARDEE specifically certifies that neither it nor any person to be paid from funds under this Agreement is delinquent in repaying any U.S. Government debt as defined by Office of Management and Budget (OMB) Circular A-129.
- d. Misconduct in Science. Compliance with Final Rule as published at 70 CFR 37010, May 17, 2005, which in Spain corresponds to Subpart A of Part 50 of Title 42 CFR, as well as the Final Rule published in 32446 if Title 54 CFR on August 8, 1989.
- e. Restrictions on Lobbying. Compliance with PL 101-121, Title 31, Section 1352, which prohibits the use of U.S. Government funds for lobbying on connection with this particular Agreement.
- f. Conflict of Interest. Compliance with the National Institutes of Health (NIH) requirement to maintain a written standard of conduct and comply with 42 CFR Part 50, Subpart F.

**10. Site Visits and Programmatic Audits.** Designated representatives of [CENTRAL OFFICE], and/or the federal government may inspect and review progress of the work performed pursuant to the Agreement and for compliance with NIH/NINDS rules and regulations and International Conference on Harmonization/ Good Clinical Practices (ICH/GCP). Access shall be granted to facilities used or otherwise associated with the work performed and to all relevant data generated under this Agreement. All such inspections shall be conducted in such a way as to not unduly delay the progress of work and [CENTRAL OFFICE] shall give reasonable notice prior to conducting such inspections. Inspection by [CENTRAL OFFICE] shall not relieve the Enrolling Center of its responsibility to fully and formally report the details of the work set forth herein.

**11. Indemnification.** [CENTRAL OFFICE], to the extent authorized under the Constitution and laws of the State of ??, shall indemnify and hold [??? UNIT] harmless from liability resulting from the negligent acts or omissions of [CENTRAL OFFICE], its agents or employees pertaining to the activities to be carried out pursuant to the obligations under this Agreement; provided, however, that [CENTRAL OFFICE] shall not hold [??? UNIT] harmless from claims arising out of the negligence or willful malfeasances of [SITE], its officers, agents, or employees, or any person or entity not subject to [CENTRAL OFFICE]'s supervision or control.

[??? UNIT] shall indemnify and hold [CENTRAL OFFICE] harmless from liability resulting from the negligent acts or omissions of [??? UNIT], its agents or employees pertaining to the activities to be carried out pursuant to the obligations under this Agreement; provided, however, that [??? UNIT] shall not hold [CENTRAL OFFICE] harmless from claims arising out of the negligence or willful malfeasances of [CENTRAL OFFICE], its officers, agents, or employees, or any person or entity not subject to [SITE]'s supervision or control.

**12. Independent Contractor.** In the performance of this Agreement, [SITE] shall be deemed an independent contractor and, as such, no employees or staff of [SITE] shall be entitled to any benefits applicable to employees of [CENTRAL OFFICE].

**13. Assignment.** [??? UNIT] shall not assign, transfer, or subcontract its interest or obligations hereunder without the written consent of [CENTRAL OFFICE].

**14. Notices.** Any notices to be given under this Agreement shall be made to the signatories of this Agreement.

**15. Termination.** [CENTRAL OFFICE] may terminate this Agreement upon thirty (30) days' written notice to [??? UNIT]. [SITE] will be reimbursed for its costs to date of termination and non-cancelable obligations properly incurred prior to the date of termination, provided, however, that such costs shall not exceed the amount allowed under this Agreement and that a report of progress to date of termination has been submitted to [CENTRAL OFFICE].

**16. Amendment.** This Agreement may be amended only by joint written agreement between the parties.

**17. Additional Provisions.** This Agreement is made because of the U. S. Department of Health Human Services, Public Health Service, National Institutes of Health (NIH) Research Project Cooperative Agreement No. ??? that was awarded to [CENTRAL OFFICE]. The general provisions of that grant are incorporated into this Agreement as Attachment C. Where there is a conflict between those provisions and this Agreement, this Agreement will govern. [??? UNIT] agrees to abide by these provisions, including the appropriate administrative and cost guidelines. Where approval is required from NIH, such approval shall be sought from [CENTRAL OFFICE]. Under no circumstances is the right to grant a no-cost extension of the termination date given to the [??? UNIT] under this Agreement.

In witness whereof, the parties hereto have executed this Agreement as of the day and year first written.

**Signatures of all parties**

**Attachment A**  
**Statement of Work**  
**Specific Activities**

Private Foundation of [SITE]  
([??? UNIT])

On behalf of [SITE], the [??? UNIT] will function as the central point of contact for administrative tasks related to [STUDY] in ???. The [??? UNIT] will act as the administrative agent of [CENTRAL OFFICE] by distributing financial reimbursement to participating Enrolling Centers in ??? and provide research data entry services for the Enrolling Centers.

**Contracting and Payment of Enrolling Centers.**

- a. Contract with Enrolling Centers on behalf of [CENTRAL OFFICE]. Such contracts shall be in conformance with the template provided as Exhibit One to this Attachment A. This template may be translated to Spanish; any translation is subject to [CENTRAL OFFICE] approval prior to execution by the Enrolling Center. Termination of contracts with Enrolling Centers can be made only at the direction of the [CENTRAL OFFICE].
- b. Issue monthly payments to the Enrolling Centers upon receipt of Reimbursement Reports from the [CENTRAL OFFICE] Coordinating Center and receipt of pass-through payment from [CENTRAL OFFICE]. Provide reconciled monthly financial disclosure of payments to Enrolling Centers, sent to [CENTRAL OFFICE] within 60 days of transacted payments.

**Data Entry and Monitoring.**

- a. Collect and/or receive case report forms from Enrolling Centers and perform data entry of patient information as described in the Manual of Operations.
- b. Respond to data queries from [CENTRAL OFFICE]-assigned Study Manager and feedback the resolution procedures to Enrolling Center(s).
- c. Monitor source documentation at Enrolling Centers at least quarterly per [STUDY] procedures and provide reports of site visits and other monitoring activities to the [CENTRAL OFFICE] Coordinating Center on a quarterly basis.

**Regulatory Documentation.**

- a. Represent [STUDY] to submit the protocol to the health ministry and centralize the IRB/EC approval process for each Enrolling Center
- b. Forward copies of all health ministry and IRB/EC approval letters with informed consent forms to the [CENTRAL OFFICE] initially and upon update.
- c. Assist Enrolling Centers to obtain NIH Federal Wide Assurance and forward copies assurances to [CENTRAL OFFICE].
- d. Assist Enrolling Center key personnel to obtain certification in Human Subjects Protection and forward copies to [CENTRAL OFFICE] Coordinating Center.

**Equipment and materials.**

- a. Receive and distribute neuropsychology materials and blood pressure equipment.
- b. Cooperate with ??? who will facilitate importation of clopidogrel and placebo from the [STUDY] Drug Distribution Center in ???.
- c. Conduct drug inventory every two weeks and enter into web-based drug inventory system to ???.

**Other.**

- a. Participate in routine conference calls with [STUDY] Coordinating Center.
- b. Provide location and amenities for training seminar to facilitate training of Enrolling Centers
- c. Provide a telephone number to site investigator for immediate contact (available 24 hours/day, 7 days/week).

Exhibit One  
Enrolling Center Template

**AGREEMENT**

This Agreement is made between the [SITE] and \_\_\_\_\_ (Enrolling Center) as a result of a subcontract from ([CENTRAL OFFICE]) and based upon a grant from the National Institutes of Health/National Institute of Neurological Disease and Stroke (NINDS) Grant No. ??? (Research Grant) award incorporated herein and attached to this Agreement to conduct a study entitled Secondary Prevention of Small Subcortical Strokes ([STUDY] Study).

**1. Key Personnel.** The [CENTRAL OFFICE] PI is ???.  
The [SITE] PI is ???.  
The Enrolling Center PI is \_\_\_\_\_.

**2. Statement of Work.** The Enrolling Center agrees to use all reasonable efforts to conduct the [STUDY] described in the Protocol incorporated herein and attached to this Agreement. The scope of work shall include screening patients, randomizing eligible patients, blood draws, the collection and submission of data, test results, radiology films, and other data as required. Any change in the Enrolling Center PI will be referred to [CENTRAL OFFICE] through [SITE] and be subject to the approval of the [CENTRAL OFFICE]. The Enrolling Center and [SITE] will ensure that IRB review is current through the study and that the research is conducted in accordance with applicable federal regulations.

**3. Reports.** The Enrolling Center shall submit any reports of unanticipated or pre-specified adverse events to the Statistical Center, within 24 hours in accordance with the requirement in the study protocol. In addition, the Enrolling Center may be asked to furnish other reports, at such times and in such form as reasonably requested by [SITE] and/or [CENTRAL OFFICE] during the term of this Agreement (e.g., progress regarding recruitment, reprints of MRI/MRA, certification of training in the Protection of Human Subjects, IRB/EC updates and renewals, FDA and Health Ministry approvals/updates, informed consent documents and other regulatory documents),.

**4. Enrollment.** The Enrolling Center agrees to enroll study participants as specified in the Protocol. The Enrolling Center shall obtain and retain in its files an informed consent for each patient enrolled. Should enrollment fall significantly below the projected enrollment rate or if the Enrolling Center consistently violates the Protocol, this Agreement may be terminated at the discretion of the [CENTRAL OFFICE] PI and in accordance with the provisions of Article 9 of this Agreement. In the event that an Enrolling Center is terminated in accordance with this Agreement, [SITE] or [CENTRAL OFFICE] reserves the right to obtain follow-up data from Enrolling Center study participants; participant consent forms should be constructed to reserve the follow-up rights of the Enrolling Center.

**5. Payment Schedule.** [SITE] agrees to make payments as follows:

Patient Costs

At randomization \$ \_\_\_\_ USD

At follow-up visit \$ \_\_\_\_ USD

(reimbursements for randomization and follow-up patient visits is contingent upon submission of data management forms to [SITE])

MRI/MRA \$ \_\_\_\_ USD

(used only in rare cases, subject to prior authorization by [CENTRAL OFFICE] PI via email)

Payments to be made under this Agreement will be generated by [SITE] when patient documents have been received and reviewed as complete in accordance with the Protocol or other payment milestones have been reached. Invoice documentation from the Enrolling Center, unless specifically requested, is not required.

Ownership of equipment supplied by [SITE] for the express purpose of this study shall remain part of [CENTRAL OFFICE] controlled assets inventory and may be subject to return upon termination or completion of the [STUDY] Study.

**6. Site Visits and Audits.** Designated representatives of [SITE], [CENTRAL OFFICE] and/or the federal government may inspect and review progress of the work performed pursuant to the Agreement and for compliance with the U.S. Food and Drug Administration, local Ministry of Health, International Conference on Harmonization (ICH) guidance and regulations for Good Clinical Practice (GCP) under Title 21 of the of the U.S. Code of Federal Regulations (CFR). Access shall be granted to facilities used or otherwise associated with the work performed and to all relevant data generated under this Agreement. All such inspections shall be conducted in such a way as to not unduly delay the progress of work and [SITE] or [CENTRAL OFFICE] shall give reasonable notice prior to conducting such inspections. Inspection by [SITE] or [CENTRAL OFFICE] shall not relieve the Enrolling Center of its responsibility to fully and formally report the details of the work set forth herein. Should the Enrolling Center receive notice of inspection or review or if it is inspected or reviewed by the U.S. Food and Drug Administration or the local Ministry of Health, the [CENTRAL OFFICE] PI shall be immediately notified.

**7. Confidentiality.** The Enrolling Center will insure that all study records will be treated as confidential and will be stored in a secure area. Study records will be stored at the Enrolling Center for at least three years after study termination. Enrolling Center agrees to be bound by patient confidentiality laws of its country and, where applicable, to the United States Health Insurance Portability and Accountability Act of 1996 (HIPAA).

**8. Publications.** Enrolling Center acknowledges that the work to be conducted under this Agreement is part of a multi-center [study] and that an independent joint publication is anticipated to be authored by the investigators in the multi-center [STUDY] Study, including the Enrolling Center PI. Therefore, Enrolling Center agrees not to independently publish the results of the [STUDY] Study, but in no event shall Enrolling Center be so restricted after expiration of twelve (12) months after completion of study enrollment at all enrolling sites, or until such time as the multi-center publication has been made.

**9. Termination.** Either party may terminate this Agreement upon thirty (30) days' written notice to the other party. Exercise by [SITE] of its rights under this Article is subject to the approval of [CENTRAL OFFICE]. Termination by either party does not relieve the Enrolling Center of the responsibilities of the follow-up phase of the Study as detailed in the Protocol. In the case of termination by [CENTRAL OFFICE], the Enrolling Center will be reimbursed for all non-cancelable commitments under Article 5, Payment Schedule.

**10. Term.** The performance of this Agreement will extend from the effective date of February 1, 2006 through January 31, 2007. Contingent upon the availability of funding, it is anticipated that the study will renew annually through January 31, 2008. However, no further funding beyond that already provided herein will be authorized without further written agreement.

**11. General Provisions.**

**11.a. Independent Contractor.** In the performance of this Agreement, Enrolling Center shall be deemed to be an independent contractor and, as such, no employees or staff of Enrolling Center shall be entitled to any benefits applicable to employees of [CENTRAL OFFICE] or [SITE].

**11.b. Assignment.** Enrolling Center shall not assign, transfer, or subcontract its interest or obligations hereunder without the prior written consent of [CENTRAL OFFICE] and [SITE].

**11.c. Notices.** Any notices due under this Agreement shall be given to the signatories of the Agreement unless otherwise stated in this Agreement.

**11.d. Amendment.** This Agreement maybe amended only by joint written agreement between the parties.

**11.e. Terms and Conditions.** It is agreed that all terms and conditions of the Research Grant will apply to the Enrolling Center in the conduct of the work under this Agreement. Where approval is required from NINDS, such approval shall be sought from [CENTRAL OFFICE] through [SITE]. Under no circumstances is the right to grant a no-cost extension of the termination date given to the AWARDEE under this Agreement.

The parties hereby accept and agree to the terms and conditions of this Agreement.

**[SITE] Project Director**

I have read this Agreement and understand my obligations hereunder.

By \_\_\_\_\_  
Name \_\_\_\_\_

Date \_\_\_\_\_

**Enrolling Center:** \_\_\_\_\_

By \_\_\_\_\_  
Name \_\_\_\_\_

Title \_\_\_\_\_

Date \_\_\_\_\_

Exhibit A—NGA plus special terms Exhibit B—Study Protocol