



National Cancer Institute-
Cancer Therapy Evaluation Program

*Cooperative Group Guidelines for the
Development, Conduct and Analysis of
Clinical Trials with International
Collaborating Institutions*



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U.S. Cooperative group members have expressed growing interest in the development of and participation in collaborative clinical trials including international cancer research institutions. NCI-CTEP has worked with the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) to seek clarification and updates on the regulatory and logistical issues that affect the design, conduct and analysis of international clinical trials that include NCI-sponsored cancer Cooperative Groups. CTEP has considered the information provided by OHRP and FDA in the formulation of the following Cooperative Group guidelines for the development, conduct and analysis of clinical trials with international collaborating institutions.

Setting up an international collaborative clinical trial.

An international collaborative clinical trial is best conducted with collaborators who have experience participating in protocol-driven clinical trials in a multi-institutional framework for the consenting and enrollment of patients, delivery of treatment, and timely reporting of toxicity and clinical data. For individual international institutions collaborating with an NCI-sponsored Cooperative Group (NCISCG), the NCISCG must identify a clinical investigator at the collaborating institution who can act as principal investigator for the international site and is responsible to effect on-site protocol regulatory approval and assumes a responsible role for all protocol patient accruals, delivery of protocol treatment, and reporting of protocol-related toxicity and clinical data. If multiple international institutions are to collaborate on the study, CTEP prefers that NCISCGs develop collaboration with a multi-institutional group (network/consortium/formal organization) that has experience conducting clinical trials together. Importantly, CTEP recommends that NCISCGs collaborate with international cooperative groups that have an identifiable and experienced coordinating center, data/statistical center, and designated chairperson or executive committee. The coordinating center for the international collaborator should act in a manner similar to the NCISCG operations office to assure proper study conduct, distribute protocol amendments, and alert institutions of protocol-related toxicity updates, etc. The international cooperative group should have formal membership criteria and clear lines of authority over its participating sites. Variations on this cooperative group model may also be acceptable and NCISCG investigators should discuss proposed scenarios with CTEP staff when an international collaborative study is under consideration.

OHRP guidelines for assurances of compliance:

The requirement for each institution engaged in human subjects research supported by the Department of Health and Human Services (HHS), including NCI-sponsored clinical trials, to hold an OHRP-approved assurance of compliance with the HHS regulations for the protection of human research subjects (45 CFR part 46) has complicated the development of international collaborations in the past. OHRP has developed the following guidelines to clarify the scenarios for which an international institution collaborating on an NCI-sponsored clinical trial would be required to hold an OHRP-approved assurance (such as a Federalwide Assurance (FWA)).

The need for international collaborating institutions to hold an OHRP-approved assurance is limited to those instances where the international institution is judged to be receiving HHS-support for their involvement in the international clinical trial. These instances include:

- (1) *HHS provides (a) direct funding to a foreign institution via a grant, contract, or cooperative agreement for the human subjects research activities; or (b) indirect funding via a subcontract executed under an HHS-supported award to a U.S. institution. The funding, whether direct or indirect, must be specifically given for the specific research trial in question.*
- (2) *HHS provides supplies, products, drugs or other tangible non-monetary items to the foreign institutions for the human subjects research activities.*
- (3) *HHS-held identifiable private data and/or identifiable specimens (i.e., data or specimens stored and maintained at an HHS owned and operated facility) is provided to foreign institution to conduct research. Only the research activities of the foreign institution(s) receiving such data and/or specimens would be considered supported by HHS. This includes analysis by a foreign institution of data obtained at U.S. institutions with HHS support.*
- (4) *Foreign institution(s) sends specimens or data collected as part of the protocol to a central laboratory or data management center for processing or analysis that will be funded or conducted by HHS, and the results from the assays or tests performed on the specimens or from the analysis of the data will be used to determine subject eligibility, study group assignment, or other aspect of the conduct of the study with respect to the involvement of subjects at the foreign institution(s).*

NCI-CTEP application of the OHRP assurance guidelines:

- (1) Direct funding or indirect funding via a subcontract would include per patient reimbursement by the NCISCG to international institutions for patient accrual, support of laboratory studies at international sites, or other study support at participating international sites.
- (2) Supplies, products, drugs or other tangible non-monetary items would include investigational agents or commercial drugs supplied to the international collaborator by NCI-CTEP.
- (3) NCI-CTEP will require that the Data Center and Coordinating Center for the international cooperative group(s) hold an OHRP-approved assurance (preferably an FWA) so that identifiable private data and/or identifiable specimens can be transferred between the NCISCG Data Center and Operations Office and the collaborating international group Data Center and Coordinating Center . (Participation by an independent single institution that directly transfers data or specimens to or receives same from NCISCG data center will necessitate that the international institution hold an FWA or other OHRP-approved assurance.)
- (4) Patient specimens or patient data from international sites that are subject to diagnostic or analytic processing in an HHS-funded laboratory or facility for purposes of determining a patient's eligibility or treatment plan will require the international institution accruing the patient to hold an FWA. (Patient specimens used for tissue banking or correlative studies are excluded.)

Recommendations for addressing the HHS regulatory requirements related to assurances when designing an international clinical study are found below. Additionally, the regulatory requirements imposed by the international collaborators' national government must also be considered during the planning of the study design and logistics.

Developing an international clinical study.

The development of the protocol scientific concept, treatment plan and study design can occur between members of an NCISCG disease committee and international collaborators representing international cooperative groups or institutions. The NCISCG disease committee is

free to engage in scientific discussions and protocol design planning without prior approval by NCI, OHRP or FDA. The interaction of the U.S. Cooperative Group members with international collaborators for purposes of protocol development does not constitute HHS support of the protocol.

The NCISCG and international collaborators should determine which group or institution will lead the study, and logistical details concerning patient registration, patient randomization, adverse event reporting and protocol data submission must be worked out by the collaborating groups. In many cases, a centralized international coordinating center and data center for each of the international cooperative groups will best serve the conduct and coordination of the clinical study. Studies including a smaller number of unaffiliated international sites may function well without a centralized approach, but each international institution responsible for data transmission to or receipt from the NCISCG must hold an FWA or other OHRP-approved assurance (see below). Web-based registration and electronic data capture can facilitate patient entry and data collection from international sites, but the patient data flow should route through the international data centers covered by an FWA.

CTEP expects that concept proposals for phase 3 and pilot studies and Letters of Intent for the conduct of studies including IND agents will be submitted by the NCISCG for CTEP Protocol Review Committee review and approval prior to the U.S. cooperative group making any commitment to trial participation. A study approved at the concept stage will not be activated until any and all protocol-specific regulatory requirements are met by all of the participating parties listed as study investigators. The NCISCG should work with the international collaborators and the CTEP liaison to determine that all identified regulatory issues are addressed or in process prior to submitting the protocol to CTEP for review. Collaborations with European Union nations require that a Clinical Trial Authorization (CTA) be submitted and approved by each individual nation prior to initiating the trial. (See below) Protocol activation of the protocol should be essentially simultaneous for all groups involved, except in cases of extenuating circumstances, which should be discussed with NCI-CTEP and any international regulatory body involved in approval of the trial or CTA.

Documentation of Institutional Review Board (IRB) or Ethics Committee (EC) approval of the protocol must be obtained by each participating institution prior to protocol activation at the institution. The IRB or EC is an independent body constituted of medical, scientific, and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of the trial protocol and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Conducting the trial.

The NCISCG and international collaborators must work closely together during the conduct of the study to assure that patient accrual, randomization, data collection and data quality control proceeds appropriately. While the accrual of patients and conduct of the protocol by collaborating international institutions does not constitute HHS-support and does not require an FWA or other OHRP-approved assurance, the NCISCG should consider the specific situations noted below that do mandate an OHRP-approved assurance for affected international institutions.

1. ***Funding of international collaborating institution by the NCISCG-*** Any arrangement resulting in funds from the NCISCG being used by international collaborating sites for the conduct of the study constitutes receipt of HHS-funds by the international site and each international site receiving funds will require an FWA or other OHRP-approved assurance. This would include funding in the form of patient capitation, support of diagnostic laboratory studies, or other activities related to the conduct of the clinical trial. The NCISCG may provide funds for central support of study conduct by providing funds to the international group coordinating center or data center, both of which are

required to have an OHRP-approved assurance. These HHS-funds cannot be used by or transferred to individual participating international sites that do not have an OHRP-approved assurance.

2. *Diagnostic studies performed by NCISCG supported laboratory affecting patient treatment on the clinical study-* Clinical studies that incorporate a diagnostic test to stratify or determine a patient's treatment on the study require that all participating sites have an FWA or other OHRP-approved assurance only if the diagnostic test is performed in an HHS-supported laboratory/facility. NCI recommends that collaborating investigators establish an international site that can perform equivalent diagnostic testing independently for international patient accruals when designing clinical studies that incorporate such diagnostics in order to preclude the HHS assurance requirement.
3. *CTEP supplied Investigational New Drug (IND) or commercial agents-* For studies that utilize IND agents secured and shipped by CTEP to participating international sites, all sites receiving the agent will require an FWA or other OHRP-approved assurance. Similarly, if commercial agents are to be supplied and shipped by CTEP to participating international sites, all sites receiving the agent will require an FWA or other OHRP-approved assurance. NCI recommends that studies involving IND agents either establish an international source and distributor of the IND agents or restrict the number of international sites to facilitate the logistics of CTEP international shipment of agent, the monitoring of agent supplies at international sites, and the extra work of supplying an IND agent subject to international regulatory issues. (See below for issues specific to European Union member states.)

Monitoring the trial.

1. *International Clinical Trial coordinated by NCISCG-* As for all NCI-supported studies (*"Essential Elements of the Data and Safety Monitoring Plan for Clinical Trials Funded by the National Cancer Institute", Version 1, April 24, 2001*), a Data Safety Monitoring Plan must be in place for each international clinical trial led by an NCISCG. The NCISCG should follow their usual monitoring procedures involving the Group Data and Safety Monitoring Board as appropriate. Prior to study activation, the NCISCG should develop procedures for notifying the international collaborators of DSMB recommendations and actions.
2. It should be noted that the NCI CTEP guidelines applied to phase 3 studies conducted in the U.S. regarding rate of protocol accrual also apply to phase 3 studies conducted with international collaboration. The following excerpt from the Cooperative Group Guidelines apply:

Early Stopping Guidelines for Slowly-Accruing Phase 3 Studies

The following early stopping guidelines for slowly-accruing phase 3 studies conducted under the NCI Clinical Trials Cooperative Group Program are stated in terms of the percentage of projected accrual during given quarter(s). For example, Quarter 5-6 accrual signifies the number of patients enrolled on trial during Quarters 5 and 6 after activation, divided by the number of patients that were projected to be enrolled during that time period based on the accrual rate specified in the protocol design. These guidelines apply only to phase 3 trials that have not had a formal interim efficacy analysis presented to the Data and Safety Monitoring Board (DSMB) before the end of the 6th quarter from study activation.

These guidelines apply to all randomized phase 3 trials that were activated after April 1, 2004.

Guidelines:

If Quarter 5-6 accrual is:

≤ 20% of projected, then stop the trial
<50% and >20% of projected, then the study team is given six (6) months to improve accrual.
If the average accrual rate in Quarter 8 is below 50% then the trial will have to be amended to reflect actual accrual. The implications of this new accrual rate on study relevance and feasibility should be discussed in the proposed amendment.

Implementation

As soon as the Quarter 5 and 6 accrual figures become available, the Group's Statistics and Data Management Center will provide to the Group Chair and the responsible NCI Program Director the average accrual for Quarters 5 and 6 (as well as the projected accrual from the protocol). The Group Chair will either close the trial or notify the investigators that they have another six (6) months in which to improve accrual according to the guidelines described above.

For trials that are closed or amended, the Group will notify the Group Data and Safety Monitoring Boards (DSMBs) of the closure or amendment at their next regularly scheduled meeting. Group Chairs may consult with their DSMB in the early closure decision, if so desired. In the unusual circumstance that the Group Chair believes that the guidelines are inappropriate for the given trial, he or she will initiate a discussion with the responsible NCI Program Director to reach a joint decision concerning what to do about the trial.

3. *International Clinical Trial coordinated by International Institution/Group-*
When a U.S. Cooperative Group participates in a clinical trial that is being coordinated by an international clinical trials organization, the international clinical trials organization will be responsible for all aspects of study monitoring including establishment and implementation of an Independent Data-Monitoring Committee. The IDMC should be established and should function in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice. Relevant sections of the Guideline for Good Clinical Practice are noted below.

Prior to the NCISCG enrolling patients in the clinical trial, the NCISCG must provide the membership of the IDMC to the CTEP Program Director for the cooperative group. A copy of the IDMC's written operating procedures and most recent report, if any, should also be provided. These documents will be maintained in the official CTEP file for the protocol. Once the clinical trial is ongoing, the international clinical trials organization is responsible for providing reports to the participating NCISCG from each IDMC meeting, at least annually (and preferably every 6 months), that summarize study accrual, adverse events, and toxicity by study arm (unless blinded study). The international clinical trials organization should also provide the NCISCG with a statement indicating that the protocol was reviewed as per the IDMC's written operating procedures and describing the IDMC's recommendations to continue, to discontinue, or to implement modifications to trial procedures. The NCISCG will make the information available for its member institutions to submit to their IRBs on an annual basis. The NCISCG will also provide these materials to the NCISCG Data Monitoring Committee (DMC).

International Conference on Harmonisation- Guideline for Good Clinical Practice

Section 1.25: Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee) An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Section 5.5.2: The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

International Conference on Harmonisation- Harmonised Tripartite Guideline for Statistical Principles for Clinical Trials

Section 4.6 Role of Independent Data Monitoring Committee (IDMC) see Sections 1.25 and 5.52 of ICH E6)

An IDMC may be established by the sponsor to assess at intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate a trial. The IDMC should have written operating procedures and maintain records of all its meetings, including interim results; these should be available for review when the trial is complete. The independence of the IDMC is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information. The IDMC is a separate entity from an Institutional Review Board (IRB) or an Independent Ethics Committee (IEC), and its composition should include clinical trial scientists knowledgeable in the appropriate disciplines including statistics.

When there are sponsor representatives on the IDMC, their role should be clearly defined in the operating procedures of the committee (for example, covering whether or not they can vote on key issues). Since these sponsor representatives would have access to unblinded information, the procedures should also address the control of dissemination of interim trial results within the sponsor organization.

4. *Radiation therapy review-* Provision should be made for the Quality Control/Quality Assurance of radiation therapy when this modality is a component of protocol treatment due to the geographic variability of radiotherapy approaches. Plans for this QC/QA should be reviewed with the Radiation Physics Center (RPC) and Quality Assurance Review Center (QARC) during protocol development for an international clinical trial.

Clinical study data analysis.

The data generated by a collaborative international clinical trial may be analyzed by a U.S. or international data center. If the data are transmitted from international collaborators to a U.S. data center for analysis, only the international data center(s) transmitting the data to the U.S. data center is required to have a FWA or other OHRP-approved assurance. Therefore, it is suggested that the international group(s) establish a central data center(s) that will receive data from all participating international sites. The central data center(s) can then transfer the data to the U.S. data center as needed. If the data is transmitted from U.S. collaborators to an international data center for analysis, only the international data center receiving and analyzing the data is required to have a FWA or other OHRP-approved assurance. The U.S. data should be sent via the NCISCG data center to the international data center.

Auditing of participating institutions

Training personnel for and assisting or participating in the conduct of audits for international sites does not constitute HHS-support to the international institutions. The specific auditing plans approved by CTEP for international participating sites are described below based on the organizational structure of the site.

Audit Methods for Studies Led by a NCISCG:

1. *International Participating Sites not in a Formal International Group or in a Network:* The Clinical Trials Monitoring Branch (CTMB) Cooperative Group Audit Guidelines (<http://ctep.cancer.gov/monitoring/guidelines.html>) are to be followed; all scheduling, preliminary reports and final reports would be reported through the CTMB Audit Information System (AIS). Each single participating site would have a separate report submitted through the CTMB-AIS. The NCISCG would be responsible, as it is in the U.S., for obtaining follow-up information and monitoring/reporting any disciplinary action, if required. This approach would be applied when a NCISCG collaborates with several individual international institutions.

2. *International Participating Sites in a Formal International Group:* Formally organized and structured international Groups (network/consortium/formal organization) with membership criteria, including a group chairman or executive committee that has lines of authority over their membership, may be audited as described below.

- a. If the international group has an established quality assurance program, the program abides by GCP guidelines or EU directives and the audit procedures closely conform to the CTMB guidelines, then the international group may audit its own members. The international group's established audit procedures would be required to be on file with the NCISCG. The NCISCG may assist the group in identifying and training personnel or may contract with a Contract Research Organization (CRO) to conduct either on-site and/or off-site audits. Audits would be conducted on-site at each participating site. If the international group has a main member/affiliate structure, affiliates could be audited off-site along with the on-site main member audit. Separate reports would be required for each audited participant. If the international group has a network or consortium structure that works with a principal investigator through a single administrative unit, then that structure can be audited as one participating site. A single audit report would be allowed. It would be the responsibility of the NCISCG to track the scheduled audits and assure that the international group has submitted preliminary reports, final reports and any required follow-up data. It would be preferable that the CTMB-AIS be used by the international group, CRO, and the NCISCG for all audit related activities. If disciplinary actions were necessary, the NCISCG would work in conjunction with the international group to carry out such actions.
- b. International groups with standardized GCP audit procedures or CROs may form audit teams to regionalize audits. Experienced large accruing participating sites who have been trained in auditing by the NCISCG or the international group would audit smaller accruing participating sites.
- c. The NCISCG may choose to audit the international group members and/or affiliates. The NCISCG would be responsible for all aspects of the audits.

3. *International Participating Sites Networked in an Informal Group:* Networked international participating sites that lack formal group infrastructures or clear lines of authority, but function within a country or region. The NCISCG may allow the networked international participating sites to form and train regional audit teams to conduct on-site audits in accordance to GCP standards and in conformance to CTMB guidelines. The NCISCG would assume all responsibility for the networked sites and would assure that all reporting is done through the CTMB-AIS. Separate reports would be required for each site audited.

Audit Method for Studies Led by an International Group:

1. *NCISCG Participating in a Clinical Trial conducted by an International Group-* If an NCISCG joins a clinical trial led by an international group, then the NCISCF would audit its own institutions using the usual CTMB guidelines and report the audit results to CTMB. The

international group would audit the international institutions according to their group guidelines and neither the NCISCF nor the international group is required to report these audit results to CTMB.

Logistical issues related to international collaborative clinical trials.

Establishment and maintenance of FWAs- The NCISCG will be responsible to assure that all FWAs or other appropriate assurances have been approved by OHRP prior to the activation of the protocol. A list of approved FWAs/assurances can be found on the OHRP website (<http://www.hhs.gov/ohrp>). A list of all international institutions requiring an FWA/OHRP-approved assurance for the protocol should be maintained by the NCISCG and provided to CTEP prior to protocol activation. It will be the responsibility of the international institutions to renew their FWAs or other OHRP-approved assurances.

Notification of International Involvement in Group Trials (Department of State Clearance)- The Group should alert the CTEP Program Specialist when a new or competing application involves any international (non-US) component. In such cases, advance clearance from the US Department of State is needed for each non-US component prior to the award. The information required by US Department of State is listed below (this information should also include all non-US subcontracts).

- Estimated annual Total Cost dollar award for the non-US component
- Name, organization, city, and country of the International (non-US) Principal or Collaborating Investigator(s)
- Biosketch and Curriculum Vitae (CV) for both the domestic Principal Investigator and the international Principal Investigator
- OHRP assurance number (i.e., Federalwide Assurance number) for the non-US component as appropriate based on description in *OHRP guidelines for assurance of compliance* (see pages 2-3).

1572 Registrations: 1572 registrations will be required for all investigators (domestic and international) enrolling patients on a clinical study under a U.S. FDA IND, whether involving investigational agents or commercial agents. International investigators participating in studies not under a U.S. FDA IND involving investigational agents obtained from distributors outside of the U.S. will not be required to submit Form 1572, but must comply with appropriate national and international regulatory requirements. Form 1572 registrations also will be unnecessary for international investigators participating in studies not under a U.S. FDA IND involving only commercial agents.

Adverse Event Reporting- Adverse events should be transmitted to the NCISCG by international centers and by NCISCG to the international collaborating centers as designated in the protocol. For studies including investigational agents, the NCISCG should submit AdEERS reports to CTEP based on the international site adverse event reports. CTEP should receive a copy of all MedWatch Forms submitted to the FDA or international drug agencies for adverse events related to commercial drugs.

Biological specimens: Regulations regarding human tissue and tumor specimen collection vary by country. The shipment of tissue and tumor samples across national borders must be planned into the protocol correlative biology procedures. Due to the variability in these procedures, tissue specimen collection may need to be an optional measure among international sites. Alternately, international satellite core laboratories could be established to collect and process specimens from international sites.

Protocol and Informed Consent translation: The conduct of a clinical trial at international sites may require the translation of the protocol document, informed consent, patient educational materials and instruments for patient-reported outcomes.

Logistical issues specific to international collaborative clinical trials performed with European Union member states.

A European Union (EU) clinical trials directive from May 2001 was implemented in May 2004 to establish Good Clinical Practice (GCP) for the conduct of clinical trials of medicinal products for human use. CTEP recommends that NCISCGs work directly with their international collaborators to assure that the necessary EU regulatory issues are addressed for each participating EU member state. Following are the several key components of the clinical trial process that NCISCGs should consider when developing an international clinical trial with EU institutions.

Clinical Trials Application- Investigators need to prepare and submit a Clinical Trials Application (CTA) for all cancer clinical trials, except those involving only products with a marketing authorization that are to be prescribed in the usual manner and used in accordance with the authorization. (Basically, all cooperative group protocols will likely require a CTA submission.) The CTA is submitted to the Competent Authority (CA) of each EU member state participating in the clinical trial in the member state's official language. The preparation, submission and verification of CA approval should be handled by the EU member state collaborating institution.

Investigational Medicinal Product- For trials involving Investigational Medicinal Product (IMP), a Qualified Person (QP) must be named to whom a Product Specification file is submitted for determination that the agent supply chain is in compliance with EU GMPs. IMPs provided from the U.S. must be shipped to European institutions via an importing facility that holds a manufacturing and import authorization license. Clinical studies of investigational agents will be more complicated due to this requirement and substantial involvement of the pharmaceutical sponsor may also be necessary. CTEP recommends that a separate EU supply and distribution of the IND agent be established by the study investigators to facilitate the development and conduct of the clinical study. CTEP Pharmaceutical Management Branch personnel should be consulted early during the development of such studies.

Ethics Committee- Investigators in each member state must designate a lead Ethics Committee that will provide a consensus opinion regarding the conduct of the trial within the member state.