JUNE 2010

REGULATORY ISSUES & MANAGEMENT

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Disclaimer

The following presentation is being given for RTOG studies only. The information represented here while current may change due to changes within RTOG internal processes or because of federal regulatory guidelines. Therefore, you may not reproduce or distribute any of the presentation without obtaining RTOG's prior written consent.

Regulatory Documents & the CTSU

Regulatory Documents

All regulatory documents for US & Canadian sites are submitted to the CTSU for cataloguing and data entry

- Continuing Reviews
- Approvals of amendments
- IRB initial study approvals
- IRB approved consent forms (translation certification)

New Process
"Broadcast June 3, 2010"
Continuing IRB Approval

- **IRB approval must continue until**
- **Finite Studies**
  - All subjects accrued have completed treatment and follow up
- **Non Finite Studies**
  - All subjects are deceased
- **Additional requirements for both finite & non finite studies**
  - No further accrual is anticipated
  - All data forms have been submitted
  - All queries to date have been resolved
  - RTOG approves the site for early closure (see form)

- **IRB approval remains necessary, even after RTOG study closure and until RTOG termination unless all the above criteria/requirements have been met**

- **Only RTOG can classify a study as "terminated" (Database lock, publication or decision not to publish)**

- **Notification of Study Termination will be received via broadcast**

- **Formal request is required for early closure when all criteria met**

New Process/Form
Request IRB Closure

RTOG Radiation Therapy Oncology Group

Request for Study Closure with Site IRB or transfer of IRB Responsibility (v.3-5-10)

A copy of both the Electronically completed signed scanned in form and the unsigned form must be sent as e-mail attachments to: RTOGREG@acr-arrs.org

IMPORTANT NOTE: Full member institutions that have affiliates that use the Full Member IRB as their IRB of record must **ensure that any and all affiliates/Joint Center institutions have also met the criteria selected below.** If they have not, then the main IRB must keep this study open for annual/continuing review until that institution has met the criteria.

Site Data Manager Contact Information:

* Name:			
* Title:			
* Phone:		* Fax:	
* E-mail:			

Institution Name: (List all Institutions covered by IRB approval that participated in the study)	**NCI Institution Code: (PAXXX)**	**RTOG Institution Number: (XXXX)**
*	*	*
*	*	*
*	*	*
*	*	*

Protocol Title	**Protocol Number: (Lead Group Number)**
*	* RTOG

* **Rationale for Study Closure (select one)**	*	**RTOG/DM Confirmation of bolded text (Approving DM Initials)**
1. **No subjects were accrued at the institution(s) listed above, and the protocol is now closed to accrual but has not been terminated by RTOG**	☐	
2A. All subjects accrued at the institution(s) listed above **are deceased for non-finite studies, all data forms have been submitted** and all queries have been resolved with no further accrual anticipated	☐	
2B. All subjects accrued at the institution(s) listed above **have completed treatment and follow up for finite studies, all data forms have been submitted** and all queries have been resolved with no further accrual anticipated	☐	
3. IRB/Ethics board responsibilities for the protocol listed above are being transferred from IRB # * _____ to IRB # * _____ and the transfer has been accepted by the new IRB. *(Please note: the new IRB of record must submit initial and continuing reviews to the CTSU using the CTSU IRB Certification form)*	☐	* **Date of IRB Action** / / (mm/dd/yyyy)

The Institutional and RTOG Staff signing below certify that the information provided above is correct

* **Typed name person completing the form:**	* **Phone:**	
	* **E-mail:**	
* **Typed name of study principal investigator:**	* **Fax:**	

* **Signature of study principal investigator:**	
	* **Date:** / / (mm/dd/yyyy)
Signature of approving RTOG Data Manager	
	Date: / / (mm/dd/yyyy)
Signature of approving RTOG Statistician	
	Date: / / (mm/dd/yyyy)
Signature of Approving RTOG Regulator	**Regulatory Approval** ☐
	Date / /

☐ Site Notification Complete Date / / ☐ CTSU Notification Complete Date / / ☐ Auditor Notification Complete Date / /

New Process
Request IRB Closure

- **Request form must be submitted to and approved by RTOG**
- **The Form has Multiple purposes**
  - Request consideration for early closure with IRB
  - Request closure with IRB when no patients enrolled on study
  - Transfer IRB responsibilities
- **RTOG response with approval of the request is required prior to taking any closure action**
- **Internal multi department review at RTOG HQ can take 7-10 business days to complete**
- **Sites will still be required to respond to queries even after study closure with the IRB**

Continuing IRB Approval

- **<u>IMPORTANT NOTE</u> Full member institutions that have affiliates that use the Full Member IRB as their IRB of record must ensure that those affiliate/ Joint Center institutions had also never put any patients on studies they are considering closing with the IRB. If they have, then the main IRB must keep this study open for annual review.**

Special Handling

- **Handling of all other study specific regulatory documentation is detailed in Sections 5.0 or 7.0 of the protocol**
  - Study Agent Shipment Form (SASF)
  - Sponsor required documentation
  - Questionnaires
  - Training Certifications
  - RT Certifications
- **Non English speaking Canadian & International sites are required to supply the CERTIFIED English translation and native language copy of the IC with their regulatory approvals**
- **Other special procedures exist for International sites**

Correlative Components

- Each participating institution must be prepared to participate in all correlative components/have a plan in place to facilitate participation and must offer every patient the opportunity to participate in these components.
- ONLY THE PATIENT can decline to participate in the correlative components of a study
- The majority of RTOG studies require varying degrees of specimen collection as part of eligibility, stratification or protocol treatment.
- Sites are encouraged to become more organized in their efforts and coordinate tissue banking collections with other protocol required specimen collections whenever possible.
- In the event tissue is collected/residing at another facility RTOG expects a good faith effort to obtain the retrospective specimens but the site will not be penalized if it is not possible.
- Prospectively the site must inform the collecting entity that future specimens collected are expected to be forwarded along with the appropriate submission form for tissue banking as noted in the protocol.

CTSU Forms & Guidance

Can be found on the RTOG website www.rtog.org under Member Info/RA Corner/CTSU

- Institution NCI codes
- IRB certification forms
- IRB transmittal forms
- Guidance for completing the forms
- Flow sheet

Proper Labeling
Ensures Proper Processing

- Please identify all information submitted to the CTSU with the institution's NCI Code on the transmittal/certification form

- If the submission covers more than one institution or an entire CCOP all assigned individual NCI institution codes covered under the approval must be listed on the transmittal/certification form or supplemental page

CTSU Forms
Transmittal/Certification

CTSU Transmittal Sheet

IRB / REGULATORY APPROVAL TRANSMITTAL SHEET

Complete this cover sheet with all submissions. **ALL FIELDS ARE REQUIRED.**
This sheet will serve as the **cover page/fax cover** for the required documents. Please forward **ALL to:** 1-215-569-0206.

Date: _____ /_____ /20_____ IRB/Regulatory Approval Transmittal Form plus (_____) page(s)
mm dd yyyy

Packet Type:
- ☐ Initial Submission
- ☐ Continuing Review
- ☐ Version/Amendment Approval
- ☐ Correction(s) from Previous Submission
- ☐ Other _____

Site/Institution: _____
Name *City* *State*

Site/Institution's NCI code: |_|_|_|_|_|_| *US Code A A # # # (2 letters, 3 numbers, eg PA999; International Code # # # # # (5 numbers, eg 99999)*

Protocol(s): _____
Full Protocol Number(s)

Attached Documents:
- ☐ CTSU IRB Certification Form or IRB Letter or HHS 310 Form
- ☐ IRB Approved Consent
- ☐ Other Items: _____

Physician of Record: _____
First name *M.I.* *Last name*

Investigator NCI Code: |_|_|_|_|_|_| *(3-, 4- or 5- digit numerical code)*

Protocol Contact at Site: _____
First name *Last name*

Phone: _____
e-mail: _____
Fax: _____

Official Use ONLY
REVIEWED BY:
Initials _____
Date _____
TID # _____

Assurance # [ ] _____ Consent Signed [ ] Stamped/Dated [ ] # of pgs _____
CTEP Site ID [ ] _____ CTEP PI ID [ ] _____
IRB Letter Signed [ ] Full Board Review [ ] Expedited [ ] Reason: _____
Appr Date [ ] _____/_____/_____ Approved for < 1 year? Expires: _____/_____/_____
Protocol Special Requirements [ ] _____ Amendment [ ] # _____

Cancer Trials Support Unit

INSTITUTIONAL REVIEW BOARD CERTIFICATION
Supplemental Page

Optional page for listing additional sites approved by the local IRB. Please indicate on certification form the number of sites listed on the supplemental form.

Mail or Fax to:
Cancer Trials Support Unit (CTSU)
ATTN: Coalition of National Cancer Cooperative Groups (CNCCG)
Suite1100
1818 Market Street
Philadelphia, PA 19103
FAX: 1-215-569-0206

In Reference to Protocol #:

Additional Institution Names (*List all additional institutions covered by IRB approval that will conduct this study.*)	**NCI Institution Code**	**OHRP assured assurance number** (include leader M – Multiple project; T – Cooperative project & FWA – Federalwide)	
Ex. University of Texas	*TX002*	*FWA*	*00000123*

Resolving Regulatory Issues

- **All issues for U.S. And Canadian sites with submitted regulatory documents should be handled directly through the CTSU.**

RTOG does not have access to copies of regulatory documents that have been submitted to the CTSU.

- **International sites should contact RTOG HQ directly**

Checking Registration Status

Visit the CTSU Website: https://www.ctsu.org/public/

- **Requires a CTSU username & password**
- **Sites are identified by NCI Code**
- **Lists all requirements for study**
- **Lists items not in compliance**
- **Not available for International sites** (outside N. America)

To obtain a CTSU password…

CTEP-AMS Fact Sheet

The Cancer Therapy Evaluation Program (CTEP) Account Management System (AMS) application is a project of the National Cancer Institute (NCI) designed to register and provide a unique identification number for all non-investigators (i.e. "Associates, Clinical Research Associates, Data Managers") participating in NCI-sponsored clinical trials through the nine adult Cooperative Groups and to establish a user account for all Investigators (i.e. physicians) and Associates. All Investigators and Associates participating in the research process through the Cancer Trials Support Unit (CTSU) are encouraged to establish a user account through CTEP-AMS. A CTEP-AMS user account will be required to access the CTSU Members web site. In addition, CTEP-AMS will allow the nine adult Cooperative Groups to claim registered Associates to their respective Group rosters.

Investigators and Associates

To obtain a valid username and password for access to the CTSU member web site Investigators and Associates must register with the CTEP-AMS registration system.

NEW Investigators

1. Log onto https://iapps-ctep.nci.nih.gov/ctepar/main.html
2. **Follow the application instructions.**
3. **You will need your NCI investigator number and a unique active email address.**
4. When you receive your CTEP-AMS approval email, click the link provided in the email and activate your account by changing your temporary password to a permanent password.
5. Congratulations!! Your application process is now complete. You may use your new CTEP-AMS user name and password to access the CTSU Members web site.
6. New investigators will be prompted to "*Check the CTSU Membership Box*" to activate their CTSU membership registration when they logon to the CTSU Members web site for the first time.

ALL Associates (Non-Investigators)

1. Log onto https://iapps-ctep.nci.nih.gov/ctepar/main.html
2. **Follow the application instructions.**
3. **You will need a unique active email address.**
4. To be considered for CTSU membership and for access to the CTSU Members web site, be sure the box "*Requested Applications: CTSU Web*" is checked.
5. When you receive your CTEP-AMS approval email, click the link provided in the email and activate your account by changing your temporary password to a permanent password.
6. Congratulations!! Your application will now be reviewed by the CTSU. You will receive an email from the CTSU providing the status of your application within 2 to 3 business days. Once you receive your email from the CTSU, you may use your new CTEP-AMS username and password to access the CTSU Members web site.

Third Party CTSU Membership Request for Physicians

If you would like to request CTSU membership for a third-party that does not have a unique email address, you can log onto the members side of the CTSU web site and click on the 'Resources' tab. Under 'CTSU applications', you will see a link for 'Third-Party CTSU Membership Request' and you can request CTSU membership for a physician that does not have a unique email address by using their NCI Investigator number. If your physician does have a unique email address, the preferred method for requesting CTSU membership is by registering on the CTEP-AMS web site. The CTSU will review the request and will inform you via email when the review process is complete.

For More Information

CTEP Registration Help Desk: 301-496-9910 (Monday to Friday 8:30am to 4:30pm Eastern Time)
Email: ctepreghelp@ctep.nci.nih.gov

CTSU Version 1/17/05

Points of Contact for the CTSU

- **Help Desk: 1-888-823-5923**
- **Regulatory Help Desk: 866-651-CTSU (2878)**
- **E-mail: ctsucontact@westat.com**
- **Fax Number: 215-569-0206**
- **Mailing Address:**

  CTSU Regulatory Office

  Coalition of National Cancer Cooperative Groups

  1818 Market Street, Suite 1100

  Philadelphia, PA 19103
- **Website: http://members.ctsu.org/**

Record Retention

According to the NCI Investigator Handbook:

- 10.3 Retention of Records

FDA regulations require that all research records (including patient charts, case report forms, x-rays and scans that document response, IRB approvals, signed informed consent documents and all agent accountability records) must be kept by the investigator for at least 2 years after an NDA or BLA has been approved for that indication or the CTEP IND has been closed. CTEP will notify investigators when these events occur. This requirement is an explicit part of the FDA Form 1572, http://ctep.cancer.gov/handbook/index.html

- For NON IND Studies:

The point of reference used to determine the length of time required for record retention for non IND studies would be RTOG's termination date for the study, which is when the database is locked and no further information would be required. The recommended timeframe for record retention is 3 years past termination The institution's (and IRB's) guidelines would also need to be considered.

Password Protected Documents on the RTOG Website

- An RTOG user name and password may be required to gain access to some password protected documents
- The username and password used for web registration will permit access to these documents
- To obtain a username & password follow the instructions on the Password Authorization Form, which can be found at the following link: http://www.rtog.org/members/webreg.html .
- The usual turnaround time for password authorization requests is two business days

the RTOG Password Authorization Form

RTOG
Radiation Therapy Oncology Group

PASSWORD AUTHORIZATION FORM

Please type all required information on this form, print the completed form and have the institutional Principal Investigator sign it and fax to RTOG Headquarters, (215) 928-0153.

Institution Name	Type Institution Name Here
RTOG Institution #	Type RTOG Number Here

I acknowledge that I will be assigned a username and password for data entry. Use of the username and password is restricted to my use for purposes of data entry for RTOG protocols. By my signature, I attest that I will maintain in confidence my assigned username and password.

Name	Type Name Here		
Role (e.g., PI, RA)	Type Role Here		
E-mail Address	Type Email Address Here		
Signature			
NIH Certification Required	*attach to form*	*attach to form*	*attach to form*
Phone #(s)	Type Phone Number Here		

Principal Investigator's Signature	
Date	

	RTOG USE ONLY		
Approved By		Date	
Issued By		Date	

Version: 02/22/2007

Informed Consent Concerns

- RTOG provides an NCI and ACR IRB Approved consent template for each protocol
- RTOG prefers no changes be made other than to add local context
- IRB requested additions to the document for clarity are permitted
- The Deletion of any information should be avoided to preserve the integrity of the document
- The essential elements of the RTOG Informed Consent Template must remain intact
- IRB required deletions of risks and alternative procedures will require written justification
- Please refer to RTOG Guidance Document for making changes to the informed consent template (recently revised)

Informed Consent Approval

- It remains your IRB's responsibility to review and approve the informed consent content and any changes made at the site level
- A CERTFIED English & native language translation of the IC is required for Non English speaking Canadian & International sites
- Please note the RTOG Regulatory Compliance Department does not review consents. All consent content will be reviewed at time of audit.
- Problems and deficiencies with IRB approved consents found during the audit will be reported as appropriate.

Broadcasts & Summary of Changes

- **Information relating to protocol updates and amendments can be found on the RTOG web site: www.rtog.org**
- **RTOG suggest sites check the website regularly to assure they have received all broadcast information**
- **NCI requires that cooperative groups provide a Summary of Changes which describes all of the changes made to a protocol, and indicates whether the changes are administrative (update) or treatment related (amendment)**
- **Under the protocols tab on the RTOG web site:**
  - There is a column for the "Summary of Changes"
  - The next column, "Broadcasts", provides all the broadcasts sent for each protocol

Finding Broadcasts & Amendments On The Website

RTOG Numeric Listing of Active Protocols - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Search Favorites

Address http://www.rtog.org/members/numericactive.html Go Links

RTOG
RADIATION THERAPY ONCOLOGY GROUP

1818 Market Street, Suite 1600
Philadelphia, PA 19103
1-800-227-5463 ext: 4189
PH: 215-574-3189 FAX: 215-928-0153

SEARCH GO

HOME | MEMBER INFO | PROTOCOLS | RESEARCH | MEETING | VISITORS | FAQ | SITE MAP

Numeric Listing of Active Protocols

Choose a study

Active Protocols

PDF FORMAT (Requires Acrobat Reader)	MISC & DIAGRAMS (That Are N/A In PDF)	SUMMARY OF CHANGES	BROADCAST
0630 Phase III (Activation: 3/25/08)	Consent & 0630 Forms	0630 Changes	0630 Broadcast
0627 Phase II GBM (Temporarily closed)	Consent & 0627 Forms	0627 Changes	0627 Broadcast
0625/ACRIN 6677 Phase II GBM (Temporarily closed)	Consent & 0625 Forms& 0625/6677 Overview& 0625/6677 ITW & 0625/6677 CRS & 0625/6677 PSA	0625 Changes	0625 Broadcast
0623 Phase II SCLC (Activation: 01/08/08)	0623 Forms & Consent & **Study Agent Shipment Form** & IND Exemption	0623 Changes	0623 Broadcast
0618 Phase II SBRT (Activation: 12/18/07)	0618 Forms & Consent		0618 Broadcast
0617 ph III NSCLC (Activation: 11/27/07)	0617 Forms & Consent	0617 Changes	0617 Broadcast
0615 Phase II Nasopharyngeal	Consent & 0615 Forms & AE Grading Tool	0615 Changes	0615 Broadcast

Done Internet

Start Inbox - Microsoft Outlo... April 2008 Microsoft PowerPoint -... RTOG Numeric Lis... Desktop 2:29 PM

Protocol Updates

- **Updates are editorial/administrative changes that RTOG is allowed to make without prior NCI approval (updates are sent to NCI for their information).**

- **Examples of protocol updates might include:**
  - correction of typos
  - changes/additions to administrative processes
  - change in the address for data submission
  - change in a Co-Chair's contact information.

- **Per NCI, an update cannot involve patient treatment or anything that would impact patient safety.**

- **The RTOG broadcasts indicate *"IRB review of an update is not required*; however, these changes must be *reported* to the site IRB"**

Protocol Amendments

- All treatment or safety related changes to protocols are amendments,
- Amendments *are sent by RTOG to NCI for review and approval*.
- As "Per CTMB Guidelines, amendments must be reviewed and approved by local IRBs within 90 days.
- For Canadian sites the broadcast of Health Canada's approval of the amendment begins the 90 day timeframe
- Full board IRB review is required If patients at the site are in active treatment on the study
- When using the CIRB, facilitated review by your local IRB may still be required for all Phase III amendments

IRB Approvals

Protocol Action	Required Type of Review
Initial Review	Full
RTOG Approved Minimal Risk Studies (as noted in the activation broadcast)	Expedited per 45 CFR 46 §46.110
Show stopper amendment	Full (90 day grace)
Update - editorial or administrative changes	Report to IRB but review & approval is not required
Continuing/Annual Reviews	
Patients in active treatment	Full
Continuing review of research previously approved by the convened IRB as follows (**8ai**) - Source: 45 CFR 46 §46.110 + Category List from OHRP	
Permanently closed to enrollment, all subjects have completed all research related interventions & research remains active only for long-term follow-up of subjects (**8a** i, ii, iii) - Source: 45 CFR 46 §46.110 + Category List from OHRP	Expedited allowed but local IRB has final authority
No enrolled subjects & no additional risks identified (**8b**) -Source: 45 CFR 46 §46.110 + Category List from OHRP	Expedited allowed but local IRB has final authority
The remaining research activities are limited to data analysis (**8c**) - Source: 45 CFR 46 §46.110 + Category List from OHRP	Expedited allowed but local IRB has final authority

- **Link to 45 CFR 46 §46.110 + Category List from OHRP Website: http://ohsr.od.nih.gov/guidelines/45cfr46.html#46.114**