WESTAT
CTSU PROCEDURE DOCUMENT

I. PURPOSE

The purpose is to document the procedures for monitoring clinical trials for all CTSU enrollments, as well as facilitate coordination of CTSU-enrolled patient cases into the adult Cooperative Group audit mechanism. The objectives are to assure compliance with Federal regulatory requirements and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity.

II. SCOPE

ICH and Federal Regulations require a standardized practice of how functions are performed and documented in a clinical trials environment. The primary source of regulated procedures is provided via SOPs generated in Westat's Clinical Trials Office, where development, oversight, maintenance, implementation and training of SOP processes are provided.

This procedure document is in compliance with Westat *SOP CL-005.1 Development of a Site Monitoring Plan.* This document provides details to the existing SOP/s to remain in compliance with corporate requirements and SOP specifications. These instructions are to be followed in addition to the relevant sections of the SOP.

This procedure applies to all cancer protocols approved by NCI/CTEP that have patient enrollment through the CTSU.

III. RESPONSIBILITY

All staff in the CTSU and Cooperative Group Audit Coordinators who perform clinical site auditing activities are responsible for complying with the Work Procedures. Project Directors and their designees are responsible for assuring compliance with the Work Procedure.

IV. REFERENCES

Code of Federal Regulations: Title 21, Parts 50, 54, 56, 312 and 314. "FDA Regulations related to Good Clinical Practice and Clinical Trials."

Office for Human Research Protection (OHRP) of the Health and Human Services (HHS), Code of Federal Regulations Title 45, part 46.

Clinical Trials Monitoring Branch, CTEP, DCTD, NCI, Guidelines for Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Clinical Trials Support Unit (CTSU), version date October 2006, effective 01Jan2007, at http://ctep.cancer.gov/monitoring/guidelines.html

Westat SOP CL-005.1: Development of a Site Monitoring Plan

Sample Audit Worksheet (SPMA-01.e1)
Attachment 1 – Endorsed Cases (SPMA-01.e2)
Attachment 2 – Non-Endorsed Cases (SPMA-01.e3)
Group Notification Memo (SPMA-01.e4)
Attachment 3 – Preliminary Report of Audit Findings (SPMA-01.e5)

V. DEFINITIONS

See CTSU Glossary for the following definitions:

Audit Information System (AIS)
Aligned Site
Audit Coordinator
CTSU Independent Clinical Research Sites (CICRS)
Clinical Trials Monitoring Branch (CTMB)
Drug Accountability Record Forms (DARFs)
Endorsed Study
Expanded Participation Project (EPP)
Institutional Review Board (IRB)
Non-Endorsed Study

VI. PROCEDURE

1. Background Information: The CTSU audit procedures are based on the Clinical Trials Monitoring Branch (CTMB)/Cancer Therapy Evaluation Program (CTEP) Guidelines (version date October 2006, effective 01Jan2007). The procedure will encompass all patient enrollments via the CTSU. The responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU.
   a. There are two distinct classes of institutions participating with the CTSU. The first are institutions that are members of an adult Cooperative Group, and the second are sites participating in the CTSU Independent Clinical Research Sites (CICRS) program.
   b. This SOP will outline the audit procedures for both types of sites.

2. Audit Obligations for Patients Registered Through CTSU: For group aligned sites, the audit of a patient registered through the CTSU is the responsibility of the group receiving credit for the enrollment. It will be vital for the CTSU Audit Coordinators to work directly with the Cooperative Group Audit Coordinator and Statistical Centers to manage the CTSU Audit Program. The CTSU obligations will vary based on the following scenarios:

CATEGORIES	TASKS	RESPONSIBILITY
CICRS Site Enrollment	Conduct the audit and all associated tasks: ▪ Selection of sites ▪ Scheduling audit dates with site ▪ Scheduling auditors ▪ Selecting protocol cases ▪ Data Points ▪ Reporting requirements ▪ Providing follow up information	▪ CTSU responsible for all aspects of the audit.
CTSU Enrollment Credited to Group on Endorsed Protocol	▪ Conduct audit of endorsed CTSU enrollment - **Group** ▪ Include CTSU cases in the regular Group audit	▪ Credited Group is responsible for all aspects of the audit. ▪ CTSU will provide a list of endorsed cases for the Group to use for case selection.
CTSU Enrollment Credited to Group on Non-Endorsed Protocol	▪ Conduct audit - **Group** ▪ Facilitate the selection of CTSU cases - **CTSU** ▪ Provide the Group with the necessary tools, i.e., CTSU site accrual reports and other audit tools – **CTSU** ▪ Provide additional audit staff if indicated - **CTSU**	▪ Credited Group will perform the audit and associated tasks. ▪ CTSU will assist as described.
Group to Group Enrollment	▪ Conduct the audit and perform all associated tasks	▪ As per current practice, the Group is responsible for all aspects of the audit.
Group to Intergroup	▪ Conduct the audit and perform all associated tasks	▪ As per current practice, the Group for which the site is a member is responsible for all aspects of the audit.

Copies of CTSU protocols, audit checklists, audit worksheets (SPMA-01.e1), patient lists and other relevant audit tools will be made available to Cooperative Group Auditors for CTSU cases.

Cooperative Group Auditors may request all of the audit preparation material listed above or a selection as needed.

3. Timing of Audits: Based on CTMB guidelines, all new member main institutions will be audited within 18 months following entry of their first patient in NCI-sponsored treatment protocols, regardless of the mechanism of enrollment. A new affiliate institution may be audited when the Cooperative Group conducts the audit of the main member institution at 36 months.
   a. Following the initial audit, all institutions will be audited at least every 36 months and are at risk for audit during any one-year. Institutions remain at risk for audit even if their membership in the Cooperative Group is withdrawn or terminated, since they have made a commitment to long-term follow-up of patients on study, with provision of good quality data according to the study schedule.
   b. Selection of terminated institutions for audit is at the discretion of the CTSU, and will focus on institutions with high accrual, particularly to important or pivotal studies and/or a large number of patients in active follow-up.
   c. CICRS sites will be audited at least once every 36 months, but may be selected for audit at any time. Additionally, any CICRS site accruing 20 or more patients within a 36 month audit cycle will be at risk for audit prior to 36 months per the CTSU Audit Panel discretion.

4. Evaluation Components: The CTSU on-site audit consists of reviewing and evaluating three components independently with compliance to CTMB and NIH guidelines for the conduct of clinical trials. The three components are as follows:

   a. IRB documentation and informed consent content
   b. Accountability of investigational agents and pharmacy operations
   c. Individual patient case records

5. Site Selection: CTSU Audit Coordinators will use the Clinical Trials Monitoring Branch (CTMB) Audit Information System (AIS) to identify which institutions are due for audit and re-audit.

   a. For Group-affiliated sites: CTSU Audit Coordinators will communicate with Cooperative Group Audit Coordinators. The CTSU will assist the Groups in identifying enrollment of CTSU patients at the sites by making CTSU accrual reports available. CTSU will provide a list of endorsed cases for the Group to use for case selection (SPMA-01.e2). CTSU will select and list the non-endorsed cases for the Group (SPMA-01.e3).
   b. For CICRS: The CTSU will coordinate the entire audit process. CTSU will schedule the audit date into the CTMB AIS at least 10 weeks prior to the audit. The CTSU will provide notice of CTSU's intent to audit the given site at least 8 weeks in advance of the audit date. The CTSU will provide the institution with a list of protocols and patient cases selected for audit review at least two but no more than four weeks prior to the audit.

6. Centralized Audits for CICRS: For all CTSU CICRS audits, the CTSU may choose to perform the audit of multiple related institutions at one central location. For any set of audits scheduled centrally, all applicable source documentation from each location must be available for audit at the central location on the day of the audit.

7. Selection of CTSU Patient Cases for Audit: CTSU Audit Coordinators will work with the Group for selection of CTSU cases and particular data items to be audited. The Groups will receive a Pre-Audit Letter (SPMA-01.e4*)* approximately 8 weeks prior to the scheduled audit. Please note- not all audits scheduled will permit an 8 week notice. However, the Pre-Audit letter will be completed and submitted to the Groups for final record retention.

    a. The CTSU Audit Coordinators receive daily CTMB AIS generated emails providing notification of scheduled Group audits.
    b. A minimum number of cases equivalent to 10% of patients accrued since the last audit will be reviewed.
    c. The 10% of cases reviewed apply to each participating site being audited.
    d. For case selection for all audits the following CTMB guidelines apply where appropriate:
        - 10% of Group / CCOP cases,
        - 10% of Group / CCOP "endorsed" cases, and
        - 10% of "non-endorsed" credited to the Group or CCOP.
        - For selection purposes, the 10% of chosen cases will always be rounded up. For example, if 12 patient cases are eligible for selection, at least two cases will be audited.
    e. When selecting cases for audit, emphasis would be given to the following types of studies: IND, multi-modality, intergroup, designated prevention trials and potential licensing trials, a well as protocol with high accrual.
    f. Selected non-endorsed cases are those cases enrolled via the CTSU at least 90 days prior to the scheduled audit date.
    g. If < 3 CTSU patients enrolled in non-endorsed studies are ***selected*** for audit at any one particular Cooperative Group member site, Cooperative Group auditors will audit CTSU cases per the Cooperative Group mechanism.
    h. If ≥ 3 CTSU patients enrolled in non-endorsed studies are ***selected*** for audit at any one particular Cooperative Group member site, CTSU auditors would augment the Cooperative Group audit team for the CTSU cases if assistance is requested by the Group Audit dates would be coordinated with the Cooperative Group Audit Coordinators. The Group may submit a request for assistance to their assigned CTSU Audit Coordinator via email.
    i. One unannounced CTSU patient case may be selected for limited audit on the day of the audit consisting at a minimum of review of informed consent and eligibility. However, if the unannounced cases only receive a limited review, then these cases do not count towards the minimum of 10%.
    j. If the Group has a need for an additional CTSU Auditor to supply expertise in certain therapeutic area not addressed by the particular group, or if the Group feels there are other circumstances which would require additional audit support, the CTSU would be willing to

consider supplementing the Group audit team on a case by case basis. The Group may submit a request for assistance to their assigned CTSU Audit Coordinator via email.

7. Selection of Material for Review: The CTSU Audit Coordinators will work with the Cooperative Group Statistical Center sponsoring the protocol to provide copies of CTSU submitted data forms to verify against the primary medical records. The submitted forms should include all data regarding eligibility and crucial outcome endpoints.
   a. IRB approvals, annual re-approvals and all required amendment approvals for all audited protocols are reviewed.
   b. A sample of at least 3 consent forms for at least three protocols will be carefully reviewed for all elements required by Federal Regulations. Of the 3 consent forms reviewed, one must be from a CTSU protocol.
   c. NCI Drug Accountability Record Forms (DARFs) for NCI-supplied agents will be reviewed where applicable. DARFs also will be crosschecked with at least 1 patient case for each of these drugs. One of the patient case DARFs reviewed must be from a CTSU case.

8. Audit Preparation at the Institution: The institution is responsible for ensuring that all relevant materials are available for review at the time of the audit. If affiliate institution records are audited at the time of the main member institution's audit, the affiliate institution must provide either the original patient source documents or copies of the complete record.

   a. This includes:
      - the Institutional Review Board (IRB) approvals, re-approvals and amendment approvals;
      - annual reports submitted to the IRB; and
      - the current version of the protocols, including any amendments and informed consents in use at the institution.
   b. Finally, all records regarding the disposition of investigational drugs, specifically copies of drug orders, return receipts, transfer forms, and the NCI DARFs, must be available. The pharmacy should be alerted that the auditors will conduct an on-site inspection of investigational agent storage and records.
      - If the physician's office, clinic or other institution receives a ***multiple day supply*** of CTEP supplied investigational agents, satellite accountability records must be maintained for each satellite site and copies must be available for review by site auditors.
   c. The Principal Investigator, or his/her designee, and the research staff should be available throughout the audit to answer any questions and help the auditors locate necessary information in the source documents. The Principal Investigator must also participate in the Exit Interview.
9. On-Site Audit Procedures Overview: Auditors will review specific data related to research and regulatory requirements during the audit. Audit checklists will be utilized to assure that all elements are reviewed. Any problems or discrepancies found are noted on the checklist, and the document must be signed by the auditors and retained by the responsible Group.

10. Review of Source Documents: Source documents should be used to independently verify study data. Source documents may include, but are not limited to, the following:

    a. Inpatient and outpatient medical records
    b. Progress notes
    c. Diagnostic reports (x-rays, scans, ECGs, etc.)
    d. Laboratory data
    e. Admission forms
    f. Study flow sheets and Protocol or Study Roadmaps that are signed and dated
    g. Appointment books
    h. Enrollment tracking sheets
    i. Subject diaries/calendars
    j. NCI DARFS
    k. Informed consents and IRB documents
    l. Copies of study forms (case report forms) that are used as source documentation must be signed and dated.

12. Assessment of Audit Findings: Each of the 3 components (IRB/informed consent content, accountability of investigational agents and pharmacy operations, and individual patient case records) is assigned an assessment based on findings at the time of the audit as follows:

    a. <u>Acceptable:</u>
        - No deficiencies identified,
        - Few lesser deficiencies identified, or
        - Major deficiencies identified during audit that were addressed and/or corrected prior to the audit for which documentation exists and no further action is required by the Cooperative Group, CCOP Research Base, the CTSU, the institution or the principal investigator.

    b. <u>Acceptable Needs Follow-up:</u>
        - Any major deficiency identified during the audit but not corrected and/or addressed prior to the audit, or
        - Multiple lesser deficiencies identified.

    c. <u>Unacceptable:</u>
        - Multiple major deficiencies identified,
        - A single major flagrant deficiency found, or
        - Excessive number of lesser deficiencies identified.

13. Exit Interview: At the conclusion of the visit, the audit team leader will conduct an exit interview with the responsible investigators and all other appropriate staff. During this exit interview, the preliminary findings and any recommendations from the audit team will be discussed. This interview provides opportunity for education, immediate dialogue, feedback, and clarification of preliminary audit findings. The audit team leader should document the

discussion in detail. This will facilitate the submission of appropriate information for the AIS final audit report to CTMB. The Principal Investigator must participate in the exit interview process.

14. Reporting Requirements: For either a Group or CTSU led audit, the responsible party must submit a preliminary report (24 Hour Report) within one working day of completing the audit to the CTMB (SPMA-01.e5).

    a. If the audit is performed by a Cooperative Group, the Group is responsible for submitting the preliminary audit report within one working day of completing the audit to the CTMB via fax.
    b. If the audit is performed by a CTSU Audit Coordinator for a CICRS audit, the CTSU will submit a **separate** report for each audited institution. The CTSU will submit the preliminary audit report within one working day of completing the audit to the CTMB via fax.

    Any major deficiencies discovered during the audit must be described in the Preliminary Report. Any findings that are suggestive of intentional misrepresentation of data, and/or disregard for regulatory safeguards for any of the three components of the audit, must be reported to the ***CTMB immediately by telephone at (301) 496-0510***.

    a. Utilizing the audit findings provided by the audit team, the Group or CTSU Audit Coordinator will enter the audit assessment information into the CTMB AIS within 70 working days of the audit date.
    b. The CTSU will submit a separate final report in the CTMB AIS for each audited institution for a CTSU CICRS audit.
    c. Once the Audit Report is finalized in AIS, the Audit Coordinator (Group or CTSU) will provide a copy of the audit report to the audit site.
    d. If a CTSU case is audited by a non-lead Group, the Cooperative Group sponsoring (lead) the protocol will be notified via email when the final audit report is available in AIS. The lead Group will be able to view the audit findings via the AIS. (Exhibit SPMA-01.e5)

15. Follow-up Requirements**:** For **each** component rated as Acceptable - Needs Follow-up or Unacceptable, the institution is required to submit a written response and/or corrective action plan to the audit coordinator within four weeks of the date the Final Report was mailed. A copy of the written response/corrective action plan, along with an assessment by the coordinating Cooperative Groups of the response/corrective action plan, must be submitted to the CTMB within 45 days of the date the final audit report was entered into the CTMB AIS.

    a. A re-audit (either internal and/or on-site) is mandatory for any component rated as **unacceptable** within 1 year or when 3-5 patients have been enrolled at the site.
    b. The CTSU reserves the right to conduct a re-audit of any of the CTSU patient cases, pharmacy and/or regulatory materials that are rated as unacceptable.

VII. DOCUMENTATION REQUIREMENTS

The following documents are required as part of the audit trail process:

a. Pre-Audit Letter to the Principal Investigator at the site announcing the date of the audit, a list of the patients and protocols to be reviewed and a description of all of the materials that must be available for review.
b. Preliminary Audit Report of audit findings submitted to the CTMB via fax within one working day of completing the audit.
c. Final Audit Report must be finalized in the CTMB AIS within 70 working days of the audit date.
d. Post–Audit Letter describing the audit findings and requesting a written response/corrective action plan for all categories labeled Acceptable Needs Follow-Up or Unacceptable forwarded to the site with a copy of the Final Audit Report.
e. Written Response/Corrective Action Plan submitted by the site to the Audit Coordinator within four weeks of the date the Final Audit Report was mailed and forwarded to the CTMB.
f. When indicated, a Follow-Up Letter will be sent to the site (copy to CTMB) after review of items contained in the Written Response/Corrective Action Plan such as challenges to audit findings with supporting documentation provided or items that may require clarification or additional documentation.

VIII. REVIEW AND REVISIONS

This procedure document will be reviewed and revised as necessary by the CTSU Project Task Manager or designee a minimum of once per six months per contract specifications.

Revision History

Version	Date	Author	Revision History Description
1	03/15/2007	Jenny Hopkins	First release for 2nd Edition of CTSU Contract No procedural changes; format/ language changes only.
2	09/14/2007	Ruth Lambersky	Second release for 2nd Edition of CTSU Contract No procedural changes; clarification of reporting requirements, centralization of audits; format/ language changes.

Reviewed by: Martha Hering **Date:** 09/8/2007

Sample Audit Worksheet

Exhibit SPMA-01.e1

PACCT-1 (ECOG) 09.19.06 v2.0

Site Visit Date:	**Patient #**	**Institution/City/CTEP#:** **Parent Institution:**	**Principal Investigator:**

CONSENT

Is written, signed and dated informed consent available?
YES NO
{ } { }

Date Consent was signed:

_____/_____/_____

Date of the version of the consent form utilized:

_____/_____/_____

Was correct version of the consent form signed:
YES NO
{ } { }

Informed Consent Comments:

PACCT-1 Audit Site Visit Report

Was second/revised informed consent signed by patient?

Randomization Date: _____/_____/_____

Program for the Assessment of Clinical Cancer Tests (PACCT-1)
Trial Assigning Individualized Options for Treatment: The **TAILORx** Trial

ELIGIBILITY CHECKLIST **Y=Yes; N=No; M = Missing Data; N/A = Not Applicable**

Eligibility Criteria (Effective 04/07/06 with Update #1) **Addendum #1 and Update #2 (09.20.06)**
(*responses must be* <u>*affirmative*</u> *if applicable*)

Selection of Patients Each of the criteria in the following section must be met in order for a patient to be considered eligible or this study. For each patient, this section should be photocopied, completed, and maintained in the patient's chart.	
• This study involves a pre-registration and a registration. All time frames for pre-study scan and lab values and other requirements will be based on the date of pre-registration.	Yes ( ) No ( )
• Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.	Yes ( ) No ( )
• Questions regarding eligibility should be directed to the ECOG Study Chair, Study Chair Liaison, or ECOG Coordinating Center.	Yes ( ) No ( )
• Patients enrolled on the PACCT-1 trial may be enrolled on other CTSU trials under the following conditions: (1) the patient has already registered on the PACCT-1 trial, (2) the treatment options in the other trials are consistent with PACT-1 specified treatment assignment (ie, chemo-hormonal therapy or hormonal therapy alone).	Yes ( ) No ( )
• Pre-registration requires a previously determined Recurrence Score (from GHI) or tissue available for submission for Oncotype DX Assay.	Yes ( ) No ( )
• If the Oncotype DX Recurrence Score was previously performed by Genomic Health, and the RS is 11-25, eligible patients may proceed from the pre-registration process to randomization within 24 to 72 hours after submission of the Oncotype DX Assay report to the ECOG Operations Office. Pre-registration may NOT be bypassed.	Yes ( ) No ( )
Pre-Registration	
1. Patients with operable histologically confirmed adenocarcinoma of the female breast who have completed primary surgical treatment and meet the following criteria: **ER and/or PR positive** Estrogen and/or progesterone receptor positive disease as defined by local pathology laboratory. ER Status: Positive ( ) Negative ( ) Indeterminate ( ) Date _____	1) Y ( ) N ( ) M ( ) NA ( )

PR Status: Positive ( ) Negative ( ) Indeterminate ( ) Date _____ **Negative axillary nodes** As assessed by sentinel lymph node biopsy, an axillary dissection, or both procedures. **Note:** As per the AJCC staging criteria, lymph nodes are characterized as positive or negative for metastases on the basis of conventional H&E staining,; lymph nodes that are negative by H&E staining and positive by immunohistochemistry (I+) or molecular techniques (mol+) are considered negative (NO). **Tumor size 1.1-5.0 (or 5 mm-1/0 cm plus unfavorable histological features)** Unfavorable features defined as intermediate or poor nuclear and/or histologic grade, or lymphovascular invasion. **Note:** Definition of tumor size: The tumor size used for determination of eligibility is the pathologic tumor size, which is usually determined by the size of the tumor as measured by inspection of the gross specimen. If the tumor size is measured microscopically and the tumor includes ductal carcinoma in-situ, the measurement should include only the invasive component of the tumor. **Her2/neu negative tumor** The tumor must be Her1/neu negative by either fluorescent in-situ hybridiation (FISH) or immunohistochemistry (e.g. 0 or 1+ by DAKO Herceptest).	
2. Patients and physician must be agreeable to initiate standard chemotherapy and hormonal therapy as adjuvant therapy. The standard chemotherapy and hormonal therapy options permitted are described in Appendix II and Appendix III.	2) Y ( ) N ( ) M ( ) NA ( )
3. A tissue specimen from the primary breast cancer has been located and is ready to be shipped to the appropriate laboratory after consent is obtained and within 3 days prior to pre-registration as indicated in Section 10. **NOTE**: For determination of the Oncotype DX Recurrence Score, tissue must be sent to Genomic Health. If the Oncotype DX Recurrence Score was previously performed by Genomic Health, tissue must be submitted to the ECOG Pathology Office upon registration.	3) Y ( ) N ( ) M ( ) NA ( )
4. Patients must be ≥ 18 years and ≤ 75 years. Age _____	4) Y ( ) N ( ) M ( ) NA ( )
5. Patients must be disease-free of prior invasive malignancies for ≥ 5 years with the exception of curatively-treated basal cell or squamous cell carcinoma of the skin or carcinoma in-situ of the cervix. Patients with a previous ipsilateral or contralateral invasive breast cancer, or with bilateral; synchronous cancers, are not eligible. Patients with previous ipsilateral or contralateral DCIS are not eligible.	5) Y ( ) N ( ) M ( ) NA ( )
6. Within 84 days from the final surgical procedure required to adequately treat the primary tumor.	6) Y ( ) N ( ) M ( ) NA ( )
7. All tumors should be removed by either a modified radical mastectomy or total excision, plus an acceptable axillary procedure (ie, sentinel lymph node biopsy, axillary dissection, or both). There must be adequate (at least 1mm, ie, ≥ 1 mm, if margin width specified) tumor-free margins of resection (for invasive and ductal carcinoma in-situ) in order for the patients to be eligible. Patients with lobular carcinoma in-situ involving the resection margins are eligible.	7) Y ( ) N ( ) M ( ) NA ( )
8. No prior chemotherapy for this malignancy.	8) Y ( ) N ( ) M ( ) NA ( )
9. No prior radiation therapy for this malignancy.	9) Y ( ) N ( ) M ( ) NA ( )
10. Patients who develop breast cancer while receiving a selective estrogen-receptor modulator (SERM; eg. tamoxifen, toremifene, raloxifene) or an aromatase inhibitor (eg. anastrazole, letrozole, exemestane) for breast cancer prevention or a SERM for other indications (eg. raloxifene for osteoporosis) are NOT eligible. However, patients may have received up to 8 weeks of a SEREM or aromatase inhibitor for this malignancy and still be eligible for study entry.	10) Y ( ) N ( ) M ( ) NA ( )
11. Patients must have an anticipated life expectancy of at least 10 years.	11) Y ( ) N ( ) M ( ) NA ( )
12. Patients with the following medical conditions should not be enrolled on this study: • Chronic obstructive pulmonary disease requiring treatment • Chronic liver disease (eg. cirrhosis, chronic active hepatitis) • Previous history of a cerebrovascular accident • History of congestive heart failure or other cardiac disease that would represent a contraindication to the use of an anthracycline (eg. doxorubicin or epirubicin) • Chronic psychiatric condition or other condition that would impair compliance with the treatment regimen	12) Y ( ) N ( ) M ( ) NA ( )
13. Women must not be pregnant or breastfeeding. A negative urine or serum pregnancy test is required for women of childbearing potential within 14 days prior to pre-registration. Female of childbearing potential Yes ( ) No ( ) Date of negative pregnancy test _____	13) Y ( ) N ( ) M ( ) NA ( )

14. Women of childbearing potential and sexually active males are strongly advised to use an accepted and effective method of non-hormonal contraception.	14) Y ( ) N ( ) M ( ) NA ( )
15. Patients must not have previously had the Oncotype DX Assay performed, with the exception of patients who have had the assay performed and have a Recurrence Score of 11-25.	15) Y ( ) N ( ) M ( ) NA ( )
16. Patients must have adequate organ function, including the following within 4 weeks prior to pre-registration:	16) Y ( ) N ( ) M ( ) NA ( )
• WBC $\geq$ 3,500 /mm³ Result _____ Date _____ • Platelets $\geq$ 100,000 /mm³ Result _____ Date _____ • SGOT (AST) < 3.0x ULN (ULN _____) Result _____ Date_____ • Serum Creatinine $\leq$ 1.5 mg/dL Result _____ Date_____	
Registration At the time of registration, information that will be required for proper stratification will include tumor size, menopausal status, and planned chemotherapy. Oncotype DX assay result _____	Yes ( ) No ( )
NOTE: Pathology blocks are to be submitted no later than 3 days following pre-registration as outlined in Section 10.1.	

Patient is (check one)
Eligible ( ) Ineligible ( ) Questionable eligibility ( ) Lacks documentation for eligibility

Comments:

STUDY PARAMETERS (Time & Events)

- Pre-study CBC (with differential and platelet count) and all required pre-study chemistries should be done ≤ 4 weeks before pre-registration.
- When recording pre-study results on ECOG Baseline Data Form, please make sure that ALL relevant dates are clearly given. Record actual dates.

REQUIRED GUIDELINES	Pre-Registration	Follow-Up [4]
History & Physical Examination	X	Every 3-6 months x 5 years, then annually thereafter
Disease & Survival Status		X [1]
Height	X	
Weight	X	
Complete Blood Count	X [2]	
Serum Creatiinine	X [2]	
AST	X [2]	
Mammography	X [3]	Annual
Oncotype DX Assay (RS score) [5]	X	
Biological Material Submission [6]	See Section 7.2	See Appendix IV

NOTES:

1 The following events must be reported to ECOG within 30 days that they are known to have occurred:

- Death from any cause
- Recurrence (ipsilateral breast tumor recurrence, local/regional recurrence, or distant recurrence), or second primary cancer.
- If these events have not occurred, follow-up at the time points indicated for history and physical exam is required to confirm that they have not occurred.

2 Obtained within 4 weeks of pre-registration.

3 Mammogram obtained as part of the original diagnosis, biopsy, and surgical treatment will suffice and need not be repeated.

4 Follow-up for up to 20 years.

5 Oncotype DX Assay (RS Score) is performed by Genomic Health. FAX a redacted copy of report to ECOG. Registration / randomization may proceed 24 hours and up to 72 hours after submission of the patient report to ECOG. Submission of primary tumor tissue is mandatory.

6 Materials submitted for banking for possible future use are to be submitted after randomization / registration, prior to the start of therapy. Submit only from patients who have given written consent for banking.

Were all Required Pre-Entry Studies appropriate prior to randomization? YES. NO. If No, Explain.

Were all Required Treatment Studies appropriate during Chemotherapy and Radiation Therapy, as specified? YES. NO. If No, Explain.

Were all Required Follow-up studies appropriate during Follow-Up, as specified? YES. NO. If No, Explain.

Were Tumor Specimen and Blood Samples obtained and submitted per protocol, as specified? YES. NO. If no, explain.

ELIGIBILITY

- ER-Positive and/or PR-Positive Breast Cancer
- Axillary Node Negative
- Candidate for Adjuvant Cytotoxic Therapy in Addition to Hormonal Therapy

STRATIFICATION

- Tumor Size: ≤ 2.0 cm vs. ≥ 2.1 cm
- Menopausal Status: Post-Menopause vs. Pre- or Peri- Menopause

- Planned Chemotherapy: Taxane containing vs. Non-taxane containing
- Planned radiation therapy: Whole breast, with no boost planned vs. Whole breast, with boost planned vs. Partial breast irradiation planned vs. No planned radiation therapy

TREATMENT PLAN

Patients must not start protocol treatment prior to registration / randomization.
Treatments should begin within 14 days after registration / randomization.

- For patients randomized or assigned to receive chemotherapy, chemotherapy should be administered first; hormonal therapy should begin within 4 weeks after the last dose of chemotherapy, and should not be given concurrently with chemotherapy.
- Patients who have had breast conservation surgery will be treated with radiotherapy. Guidelines for RT are as follows:
    a. Irradiation should begin within 4 weeks of registration for patients receiving hormonal therapy alone or within 4-8 weeks after completion of chemotherapy (or sooner if the patient has adequately recovered from chemotherapy-associated toxicity.
    b. External beam irradiation to the whole breast is advised to a dose of 45-50 Gy. A boost dose to the primary tumor bed may be delivered at the discretion of the treating physician to bring the total dose to 60-66 Gy. Patients may receive partial breast radiation if they are participating in NSABP and/or RTOG partial irradiation trials.
    c. Concurrent treatment: Irradiation should not be given concurrently with chemotherapy. Irradiation will be given concurrently with hormonal therapy. Hormonal therapy should not be delayed until the completion of irradiation.

Arm A
Secondary Study Group – 1 (Recurrence Score < 11)
Hormonal Therapy Alone – Physician Choice

Arm B - Randomized
Primary Study Group (Recurrence Score 11-25)
Hormonal Therapy Alone – Physician Choice

Arm C - Randomized
Primary Study Group (Recurrence Score 11-25)
Chemotherapy Plus Hormonal Therapy – Physician Choice

Arm D
Secondary Study Group – 2 (Recurrence Score >25)
Chemotherapy Plus Hormonal Therapy – Physician Choice

Refer Appendix II for Chemotherapy Regimens and Appendix III for hormonal Therapy Regimens.

Was Chemotherapy and/or Hormonal Therapy administered as indicated above? YES. NO. If No, Explain.

Was drug administration cross checked against the NCI Drug Accountability Record Forms (*DARFs*)? YES. NO. N/A. If No, Explain.

NA
********** Commercial agents used.*********

ADVERSE EVENT REPORTING
Refer to Section 5.3.

All toxicities should be graded according to the Common Toxicity Criteria Version 3.0.

Were toxicity management and dose modifications appropriately undertaken throughout the study? YES. NO. N/A. If No, Explain.

Were all serious Adverse Experiences properly reported in accordance with the protocol? YES. NO. N/A. If NO, list the type and severity of unreported toxicities below.

Were all serious ADRs reported to ECOG and/or CTSU? YES. NO. N/A

Were all serious ADRs reported to the Local IRB? YES. NO. N/A

OBJECTIVES

Primary

- To determine whether adjuvant hormonal therapy is not inferior to adjuvant chemo-hormonal in women whose tumors meet established clinical guidelines for adjuvant chemotherapy and fall in the "primary study group" category. The primary endpoint is disease-free survival; other co-primary clinical endpoints include distant recurrence free interval, recurrence free interval, and overall survival.
- To create a tissue and specimen bank for patients enrolled in this trial, including formalin fixed paraffin embedded tumor specimens, tissue micro-arrays, plasma, and DNA obtained from peripheral blood.

Secondary

- To determine whether adjuvant hormonal is sufficient treatment for women whose tumors meet established clinical guidelines for adjuvant chemotherapy and who fall into the secondary study group-1 category. The primary endpoint is disease-free survival; other co-primary endpoints included distant recurrence free interval, recurrence free interval, and overall survival.
- To determine the outcomes projected at 10 years by adjuvant, with those made by Genomic Health Oncotype DX Assay.
- To estimate failure rates as a function of RS separately in the chemotherapy and no chemotherapy arms (groups).
- To determine the prognostic significance of the Oncotype DX recurrence score and of the individual RS gene groups.

Were outcomes of recurrence or measurements of effect documented per protocol requirements? Yes. NO.
If No, explain.

DATA SUBMISSION

Follow guidelines in Section 11.0

Assess the Overall Patient Case Review audit findings for this patient as follows:

{ } Acceptable
{ } Acceptable, Needs Follow-up (Comment below)
{ } Unacceptable (Comment Below)

Comments:

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Attachment #1 Endorsed Cases

Endorsed Cases (audit is responsibility of credited group) for (NCI Site Code):

NCI Site Code:
Name of Institution:
Audit Date: 3/23/04
Audit Location: on site

Total Number of ECOG Endorsed cases = 6
Protocol Number C40101 (5 cases)
Protocol Number NCIC.BR.19 (1 case)

Protocol #	PID #	Treating MD	Treatment Arm	Registration Date
C40101				
C40101				
C40101				
C40101				
C40101				
NCIC.BR.19				

Note: ECOG to choose the above noted ECOG endorsed CTSU case(s) for (NCI Code) ECOG audit. The minimum number of total cases reviewed will still be equivalent to at least 10% of non-endorsed, credited cases, 10% endorsed, credited cases and 10% Group cases accrued since last ECOG audit for this site. After selecting the case(s), please inform your CTSU Audit coordinator and they will contact the respective Cooperative Group for copies of the case report forms for the audit.

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Attachment #2 Non-Endorsed Cases

Non-Endorsed Cases (audit responsibility of credited group for < 3 enrollments selected) for (NCI Code):

NCI Site Code:
Name of Institution:
Audit Date: 3/23/04
Audit Location: on site

Total Number of ECOG Non-Endorsed cases = 11
Protocol Number: GOG-0182 (2 cases)
Protocol Number: S0003 (3 cases)
Protocol Number: S0012 (3 cases)
Protocol Number: S0023 (3 cases)

CTSU has selected the following non-endorsed case for audit:

Protocol Number: S0023*
PID Number:
Treating MD:
Registration Date:

*All audit categories must be reviewed for this protocol, including Accountability of Investigational Agents and Pharmacy Operations. If there is more than one protocol reviewed in the non-endorsed case review, at least one of the ICC, Accountability of Investigational Agents, and Pharmacy Operations reviewed must be a CTSU protocol.

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Sample Group Notification Memo

(insert date)

Group Contact Name
Audit Coordinator
Address

Re: Cancer Trials Support Unit (CTSU) review of enrollment by_____(List NCI Codes) for (insert Group Name) _____ audit

Dear (insert Audit Coordinator's Name or Contact's Name):

We have reviewed the Clinical Trials Monitoring Branch (CTMB) Audit Information System (AIS), for the _____ (insert NCI Codes) scheduled and/or discussed for the above noted site(s). As you know, per the CTSU Work Instruction Number 05.02.WI.01: 'For Group aligned site(s), the audit of a patient registered through CTSU will become the responsibility of the Group receiving the credit for the enrollment'. CTSU will identify all respective credited Group non-endorsed enrollments and select the specific cases for audit. For convenience, CTSU will also identify the respective Group credited endorsed enrollment. However, it will be the responsibility of the Group to select the endorsed cases for any given audit

For case selection for all audits, CTMB (NCI) recommends a sampling stratification for 10% of Group cases, plus 10% of endorsed cases (where applicable), plus 10% of non-endorsed cases (where applicable). These guidelines were outlined in the CTMB Audit Guidelines (version October 2006) and have been incorporated in the April 2007 CTSU Work Instruction Number 05.02.WI.01. For the audits identified, CTSU has selected the non-endorsed cases (attachment #1). The CTSU has also included the (insert Group name) _____ endorsed case(s) and audit selections (attachment #2).

In order for CTSU to obtain the charts in a timely manner, please provide the endorsed audit case selection by _____, 2007. Please also indicate who should receive the audit material and delivery location.

The audit results of the CTSU cases will be reported directly to CTMB (NCI) via AIS on your Group audit report for the respective sites.

Please contact me at _____ (insert phone #) or _____ (insert email address) if I can be of further assistance.

Thank you for your continued support and participation in the CTSU.

Sincerely,

Name
Title
Enc.

Cc: Ruth Lambersky, CCRP (CTSU)