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SPMA.02: Maintaining Audit Worksheets

Project Name: Cancer Trials Support Unit (CTSU)

Project Director: Steve Riordan

Effective Date: 08/30/2012

DOCUMENT CONTROL

Change Record:

EFFECTIVE DATE	AUTHOR	VERSION	CHANGE HISTORY LOG
04/13/2007	Jenny Hopkins	01	First release for 2nd Edition of CTSU Contract
10/15/2007	Ruth Lambersky	02	No changes.
04/28/2008	Ruth Lambersky	03	No changes.
09/22/2008	Ruth Lambersky	04	No changes.
12/15/2008	Ruth Lambersky	05	Removed EPP from definitions list.
06/01/2009	Ruth Lambersky	06	Minor clarification of location of web site postings.
12/15/2009	Ruth Lambersky	07	No changes.
06/15/2010	Ruth Lambersky	08	Minor changes to list of trials with audit worksheets and revision process.
12/15/2010	Ruth Lambersky	09	No changes.
06/10/2011	Ruth Lambersky	10	No changes.
12/15/2011	Ruth Lambersky	11	No changes.
08/30/2012	Brenda McCalister-Afflick	12	Minor editorial updates. Removed CICRS from the definitions list.

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WESTAT
CTSU PROCEDURE DOCUMENT

CTSU Procedure: SPMA.02
Title: Maintaining Audit Worksheets

I. PURPOSE

The purpose is to document the procedure for maintaining audit worksheets developed by Cancer Trials Support Unit (CTSU) staff and for use by the CTSU audit staff, Cooperative Group audit staff and as reference materials for institutional staff when posted on the CTSU member's web site.

II. SCOPE

This procedure applies to all currently active CTSU menu protocols defined as: all Adult Cooperative Group treatment trials and all DCP Cancer Control Trials.

III. RESPONSIBILITY

- The CTSU Lead Audit Coordinator or designee is responsible for ensuring compliance with this procedure.
- The CTSU Audit Task Lead or designee is responsible for overseeing this procedure.
- The CTSU Audit Task Lead and the CTSU Project Director or their designees are responsible for ensuring compliance with this procedure.

IV. REFERENCES

- CTSU Procedure SPMA.01.12: CTSU Auditing Procedures
- Clinical Trials Monitoring Branch (CTMB), Cancer Therapy Evaluation Program (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/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm
- Sample Audit Worksheet (Exhibit SPMA.02.12.e1)

V. DEFINITIONS

See CTSU Glossary for the following definitions:

- CTSU Lead Audit Coordinator
- Clinical Trials Monitoring Branch (CTMB)
- Drug Accountability Record Forms (DARFs)
- Institutional Review Board (IRB)

VI. BACKGROUND

The CTSU audit procedures are based on the Clinical Trials Monitoring Branch (CTMB)/Cancer Therapy Evaluation Program (CTEP) Guidelines (version date October 2006). Audit worksheets are developed by the CTSU Audit team for each protocol (excluding correlative or ancillary studies) on the CTSU menu. The worksheets are also made available to the CTSU assigned auditors, Cooperative Group assigned

auditors and to sites participating on CTSU menu trials as reference materials in preparation for their scheduled audits.

VII. PROCEDURE

1. Evaluation Components: The CTSU on-site audit consists of reviewing and evaluating three components independently with compliance to Clinical Trials Monitoring Branch (CTMB) and National Institute of Health (NIH) guidelines for the conduct of clinical trials. Each worksheet is designed to include information on each of the three components. The three components are as follows:

    1.1 Institutional Review Board (IRB) documentation and informed consent content.
    1.2 Accountability of investigational agents and pharmacy operations (including DARFs).
    1.3 Individual patient case records.

2. Development and Maintenance of Audit Worksheets: The Audit Worksheets are developed once a protocol has been approved and placed on the CTSU menu according to the following design (excluding correlative or ancillary studies.)

    2.1 For a newly opened protocol on the CTSU menu, the audit worksheet is developed within three months of activation on the CTSU menu.
    2.2 For a protocol on the CTSU with a new amendment or revision, the revised audit worksheet inclusive of the revisions is posted within six weeks.
    2.3 All newly developed or revised worksheets are forwarded to the CTSU Web Administrator at Westat for posting on the CTSU Members' web site on the appropriate protocol page (under Miscellaneous Documents) and the Education & Resources page (in the Audit Resources → Protocol-Specified Audit Worksheets folder)

3. Evaluation of Audit Worksheet Versions: A designated CTSU audit staff member will check the posted Audit Worksheets on the CTSU web site each quarter to ensure that the current versions of all of the worksheets are posted on the web site in the appropriate place. If there are any errors in version and/or placement of the worksheets, they shall be reported as soon as possible to the CTSU Lead Audit Coordinator who will initiate corrective action.

VIII. DOCUMENTATION REQUIREMENTS

Quarterly review of all Audit Worksheets are posted on CTSU web site for accurate version and placement.

IX. REVIEW AND REVISIONS

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

Sample Audit Worksheet

ECOG PACCT-1
Addendum 2
CTSU Post Date 8/10/07

PACCT-1 / Audit Site Visit Report

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

CONSENT	**Informed Consent Comments:**
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** **{ } { }**	**Was second/revised informed consent signed by patient?**

Randomization Date: _____/_____/_____

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

Program for the Assessment of Clinical Cancer Tests (PACCT-1)
Trial **A**ssigning **I**ndividua**l**ized **O**ptions for **T**reatment: The **TAILORx** Trial

Eligibility Criteria (includes the following):
Activation Effective 04/07/06 (with Update #1)
Addendum #1 and Update #2 09/20/06
Addendum #2 09/05/07

(*responses must be affirmative 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	Yes ( ) No ( )

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 (i.e., chemo-hormonal therapy or hormonal therapy alone).	Yes ( ) No ( ) Yes ( ) No ( )
• Pre-registration requires a previously determined Recurrence Score (from GHI) or tissue available for submission for Oncotype DX Assay.	
• 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.	
Pre-Registration	1) Y ( ) N ( ) M ( ) NA ( )
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 _____ 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 hybridization (FISH) or immunohistochemistry (e.g. 0 or 1+ by DAKO Herceptest).	2) Y ( ) N ( ) M ( ) NA ( )
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.	3) 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.	4) Y ( ) N ( ) M ( ) NA ( ) 5) Y ( ) N ( ) M ( ) NA ( )
4. Patients must be ≥ 18 years and ≤ 75 years. Age _____	
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.	6) Y ( ) N ( ) M ( ) NA ( ) 7) Y ( ) N ( ) M ( ) NA ( )
6. Within 84 days from the final surgical procedure required to adequately treat the primary tumor.	
7. All tumors should be removed by a modified radical mastectomy or total excision, plus an acceptable axillary procedure (i.e., sentinel lymph node biopsy, axillary dissection, or both). There must be adequate (at least 1mm, i.e., ≥ 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.	8) Y ( ) N ( ) M ( ) NA ( ) 9) Y ( ) N ( ) M ( ) NA ( ) 10) Y ( ) N ( ) M ( ) NA ( )
8. No prior chemotherapy for this malignancy.	
9. No prior radiation therapy for this malignancy.	
10. Patients who develop breast cancer while receiving a selective estrogen-receptor modulator (SERM; e.g. tamoxifen, toremifene, raloxifene) or an aromatase inhibitor (e.g. anastrazole, letrozole, exemestane) for breast cancer prevention or a SERM for other indications (e.g. 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.	11) Y ( ) N ( ) M ( ) NA ( )
11. Patients must have an anticipated life expectancy of at least 10 years.	12) 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 (e.g. 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 (e.g. doxorubicin or epirubicin) • Chronic psychiatric condition or other condition that would impair compliance with the treatment regimen	13) 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 _____	14) Y ( ) N ( ) M ( ) NA ( ) 15) 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. 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. 16. Patients must have adequate organ function, including the following within 4 weeks prior to pre-registration: • 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 _____ **NOTE:** Pathology blocks are to be submitted no later than 3 days following pre-registration as outlined in Section 10.1.	16) Y ( ) N ( ) M ( ) NA ( ) Yes ( ) No ( )

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

Comments:

Sample Audit Worksheet

ECOG PACCT-1
Addendum 2
CTSU Post Date 8/10/07

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 Creatinine	X [2]	
AST	X [2]	
Mammography and/or Breast MRI*	X [3]	Annual
Oncotype DX Assay (RS score) [5]	X	
Biological Material Submission [6]	See Section 10	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 and/or Brest MRI 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 (see sections 4, 10 and Appendix V). 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.

* Bilateral breast MRI alone is acceptable if mammography could not be performed.

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: $\leq$ 2.0 cm vs. $\geq$ 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 (*DARF*s)? 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.

- Arms A-D using AdEERS.
- Any Grade=5 with an attribution of Possible, Probable or Definite must be reported via the AdEERS system.
    - Report required within 7 calendar days of learning of the event.
    - Any death within 30 days of the last dose of treatment regardless of attribution must be reported with 7 calendar days of learning of the event.

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.

MEASUREMENT OF EFFECT See Section 6.0

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

Sample Audit Worksheet

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

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

Comments: