American College of Surgeons Oncology Group

Z0011

A randomized trial of axillary node dissection in women with clinical T1 or T2 N0 M0 breast cancer who have a positive sentinel node

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The Following Groups Have Endorsed This Trial:

- **NCCTG:** Co-chair Barbara Pockaj, MD
- **NSABP:** Co-chair Thomas Julian, MD

All Cooperative Group members who are not aligned with ACOSOG will enroll patients to this study via the Cancer Trials Support Unit (CTSU).

Copy the ACOSOG QA Specialist on all correspondence.

- For patient eligibility or treatment-related questions, send an email to the ACOSOG Study Chair(s). No exemptions or waivers will be granted for patients who do not meet the eligibility criteria.
- For forms –specific questions, send an email to the ACOSOG QA Specialist.
- For specific statistical questions, send an email to the ACOSOG Statisticians.
- For all other questions, contact the ACOSOG QA Specialist by phone or email. All calls and correspondence will be triaged to the appropriate representative.

ACOSOG Standard Operating Procedures (SOPs)

For detailed guidelines for the conduct of this study, sites should refer to the following SOPs available from the ACOSOG website at http://www.acosog.org:

SOP Name	Description
DataSub	Data Submission
Death Notice	Notice of Death
DFQC	Data Fax Quality Control
ExtFU	Extended Follow-up
ImageRevSub	Image Review Submission
InfCon	Informed Consent Procedures
IRB App	Institutional Review Board Approval
OHRP	Applying for OHRP Assurance
Pat Reg	Patient Registration
StAmRev	Study Amendments and Revisions

Cancer Trials Support Unit (CTSU) Address and Contact Information

To submit site registration documents: For patient enrollments: CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206 CTSU Data Operations Center Phone – 1-888-462-3009 Fax – 1-888-691-8039 Westat CTSU Data Operations Center 1441 W. Montgomery Avenue Rockville, MD 20850-2062
To submit study forms or data: Fax to 507-293-3575.
For patient eligibility or treatment-related questions contact the ACOSOG Study Chair and copy the ACOSOG Study Coordinator. The option remains to contact CTSU Help Desk for assistance in obtaining a response from the Group.
All other questions (including forms -specific questions) should be communicated by phone or e -mail to the CTSU Help Desk at: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.
The CTSU Public Web site is located at: www.ctsu.org The CTSU Registered Member Web site is located at http://members.ctsu.org

CTSU logistical information is found in Appendix 15.4.

Participants:

- American College of Surgeons Oncology Group (ACOSOG) Members
- North Central Clinical Trials Group (NCCTG) Members
- NCI Cancer Trials Support Unit (CTSU) investigators. Note that patient enrollments from North American clinical sites that are not aligned with ACOSOG or NCCTG will be conducted via the Cancer Trials Support Unit (CTSU) and all data should be sent to the CTSU.

The CTSU will use the *ACOSOG-Z0011* protocol number as required for reporting to ACOSOG and NCI, and when registering patients through the ACOSOG Registrar. CTSU participants and institutions will be instructed to use the *ACOSOG-Z0011* protocol number on all data forms.

Table of Contents

1 Introduction

1.1 Background

Women with clinical stage T1 or T2 N0 M0 breast cancer will undergo sentinel lymph node dissection (SLND) with breast conserving therapy (BCT). Women who are found to have a sentinel node (SN) containing metastatic breast cancer as documented on frozen section, touch prep, or permanent section evaluation by hematoxylin and eosin (H&E) staining will be randomized to receive either completion axillary lymph node dissection (ALND) or no immediate additional axillary surgery or axillary-specific radiation. Subsequently, women in both Arms will then have whole breast radiation therapy and, if indicated, systemic adjuvant therapy.

1.1.1 Axillary Lymph Node Dissection (ALND)

Although axillary lymph node dissection (ALND) has been used in the management of breast cancer for at least a century, its role is controversial. The status of the axilla is an important prognostic indicator and has been the mainstay for accurate staging of patients with breast cancer. The NIH Consensus Conference in 1990 recommended that Level I and II ALNDs be routine for staging and regional control for patients with early breast cancer [NIHCC 1991]. Since ALND is associated with significant morbidity, some have tried to develop less invasive procedures to identify axillary metastases. However, at present, no existing imaging modalities or biologic markers can successfully identify patients with axillary metastasis with sufficient sensitivity to be used clinically.

1.1.2 Sentinel Lymph Node Dissection

Morton et al. popularized SN lymphatic mapping for patients with malignant melanoma [Morton 1992]. A SN is the first lymph node that drains a particular cancer into the lymphatic system and thus, histopathologic examination may determine the status of the lymphatic basin. Giuliano et al. applied this dye technique to patients with early stage breast cancer [Giuliano 1994]. In the most recent series of patients, the SN was successfully identified in 93% of the patients and it was 100% predictive of nodal status [Giuliano 1997]. Others have had similar success with the identification of SNs in breast cancer using a variety of agents such as isosulfan blue dye, radioactive colloid or a combination of both [Krag 1993, Veronesi 1997, Albertini 1996]. SLND is able to accurately stage breast cancer tumo rs by identifying those with axillary metastasis, and may offer an alternative to ALND.

1.1.3 The Need for Axillary Lymph Node Dissection

Axillary metastasis traditionally has dictated the need for systemic adjuvant chemotherapy or hormonal therapy. Over the past few years, more attention has been focused on the characteristics of the primary tumor. The need for chemotherapy is often based solely on the size of the primary tumor and its biologic characteristics. Therefore, at present, many women receive adjuvant chemotherapy despite a negative axilla. This brings into question the continued need for an immediate axillary dissection.

The ALND has a role in staging, regional control, and perhaps survival. The presence or absence of lymph node metastases in the ALND determines stage, not necessarily the number of positive nodes [Beahrs 1992]. ALND offers excellent regional control. Axillary recurrences after ALND for clinically node-negative women are extremely unusual and are in the order of 12% [Ivens 1992]. The impact of ALND on survival is perhaps the most controversial aspect. Originally, it was assumed, because of the Halstedian concept of the biology of breast cancer, that en-bloc resection of the regional nodes improved survival by complete removal of local and regional tumor. Since then, numerous studies and observations have invalidated the Halstedian concept itself as well as the impact of axillary surgery on survival. However, the data are conflicting and numerous well recognized studies have raised unanswered questions related to whether ALND itself affects survival.

A number of studies epitomized by the prospective randomized trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 Trial, have shown no impact of ALND on survival [Fisher 1985]. In the NSABP B-04 trial conducted in the early 1970's, patients were randomized to radical mastectomy, total mastectomy, or total mastectomy plus post-operative radiation therapy to the chest wall and regional lymph nodes. In the radical mastectomy group, 38% of patients were found to have tumor-involved lymph nodes. Since this was a randomized trial, it could be assumed that 38% of patients in the other two arms had tumor-involved lymph nodes. However, the regional recurrence rate after total mastectomy alone, with no regional axillary therapy, was only 18 percent and the regional recurrence rate after axillary radiation therapy

without axillary surgery was only 2 percent. In addition, there was no statistically significant effect of loco-regional control on survival. Patients who developed an axillary recurrence after total mastectomy alone were treated with a delayed ALND. All three arms had similar survival rates, with follow-up as long as 15 years. This study forms the most solid basis for those who believe ALND offers no beneficial effect on survival. Table 1 lists other studies supporting the concept that loco-regional control through ALND or radiation therapy does not affect survival.

Table 1: Studies showing no effect of loco-regional control on overall survival

Study	Date	n	Treatment arms	Survival differences
NSABP B04 [Fisher 1985]	1977	1159	Radical Mastectomy (RM) vs. Total mastectomy (TM) vs. TM and radiotherapy (RT)	Not significant
Cancer Research Campaign [CRCWP 1980]	1980	2243	TM vs. TM+RT	Not significant
Manchester Trial [Cythgre 1982]	1982	1022	TM vs. TM+RT	Not significant
Glasgow Trial [McArdle 1986]	1986	322	Post-op RT + Chemo vs. RT alone	Not significant
NSABP B06 [Fisher 1989]	1989	1843	TM vs. Lumpectomy vs. Lumpectomy + RT (all had ALND)	Not significant
Stockholm Trial [Rutquist 1993]	1993	644	Modified RM (MRM) vs. MRM +RT	Not significant

The contrary viewpoint supports the importance of ALND, suggesting that inadequate loco-regional control adversely affects survival. One of the best known of these studies is the Second Guys Hospital Trial [Hayward 1981]. This trial was randomized, comparing women treated with radical mastectomy and regional lymphatic radiation to those treated with local excision of the primary breast tumor and radiation therapy to the breast and regional lymphatics. The radiation therapy used in this trial was only 3,000 centigray to the regional lymphatics. This is now recognized to be an inadequate dose. The patients treated with radical mastectomy had a 2.0% axillary recurrence, whereas those treated with no axillary surgery and inadequate radiation therapy had an 11% axillary recurrence rate. These two groups had statistically significant differences in local control, regional control, and in overall survival. The increased axillary recurrence in the group receiving no ALND was associated with a significant diminution of overall survival by about 10% compared to those women treated with radical mastectomy. This effect has persisted for at least 20 years, suggesting that effective breast and axillary treatments may be associated with an enhancement in overall survival. Table 2 lists other studies supporting the concept that loco-regional control through ALND or radiation therapy does affect survival.

Table 2: Studies showing effect of loco-regional control on overall survival

Study/Trial	Date	n	Treatment arms	Survival differences
Guys Hospital [Hayward 1981]	1981	253	Radical mastectomy (RM) vs. Wide local excision (WLE)+RT	Significant at 20 yrs.
Southeast Scotland (Edinburgh Trial) [Langlands 1980]	1980	275	RM vs. TM+RT	Not significant at 5 yrs. Significant at 8 yrs.
Cabanes [Cabanes 1992]	1992	658	Lump+RT vs. Lump+RT+ALND	Significant
White [White 1996]	1996	1126	Lump+RT vs. Lump+RT+ALND vs. MRM	Significant
Overgaard* [Overgaard 1997]	1997	1708	MRM+RT+CMF vs. MRM+CMF	Significant at 10 yrs. (OS)
Ragaz* [Ragaz 1997]	1997	318	MRM +RT+CMF vs. MRM+CMF	Significant at 10-15 yrs. (DFS)

*Pre-menopausal only

1.1.4 Treatment and Survival Following Axillary Recurrence

While the adverse effect of loco-regional recurrence after total mastectomy (TM) for breast cancer has been recognized, the impact of loco-regional failure after breast-conserving surgery and radiation is less clear. Of the patients with loco-regional failure after BCT, only 5% to 15% present with concurrent distant metastases [Fowble 1990, Haffty 1991, Recht 1989, Fourquet 1989, Stotter 1989]. In contrast, up to 25% of patients who present with loco-regional failure after TM have concurrent distant metastases or develop distant metastases within a few months of the loco-regional failure [Andry 1989, Marshall 1974, Aberizk 1986]. In the Danish trial by Overgaard et al., 41% (31 / 75) of loco-regional failures in the RT + CMF arm failure, as well as 20% (56 of 277) in the CMF alone arm, presented with concurrent distant metastases [Overgaard 1997]. In addition, outcomes after aggressive salvage of loco-regional failure also are different between TM and BCT patients. In a series of patients at the Joint Center for Radiation Therapy (JCRT) with loco-regional failure after TM, the 5 and 10-year actuarial rates of freedom from distant metastases were 30% and 7%, respectively. In contrast, patients with salvage TM after BCT and loco-regional failure at JCRT had a better prognosis [Abner 1993]. The 5-year actuarial rate of further recurrence in this group was 37%, and the 5-year cause-specific survival was 79%. Similar results for BCT loco-regional failure salvage have been reported from the University of Pennsylvania [Orel 1993]. Thus, the prognostic significance of loco-regional failure may not be the same between patients receiving TM and BCT.

1.1.5 SLND Only Versus ALND

A major problem with the majority of studies examining the impact of axillary node dissection on survival is inadequate sample size and/or follow-up. Studies of surgical therapy alone demonstrate that 50% of patients with nodal metastasis survive 20 years. Since only about 35% of clinically node-negative breast cancers have axillary node metastasis, at best we could expect only about 17.5% of the patients to have a chance to be affected by interventions studied (50% of the 35% patients who are node-positive). The majority of studies had insufficient statistical power to detect a difference in survival related to ALND.

Some reasons that SLND may replace ALND relate to the biology, epidemiology, and screening of breast cancer. Due to increased public awareness and improved screening, there has been a decrease in the mean maximum diameter of breast cancer tumors and a concomitant decrease in the number of women with lymph node metastasis [Tabar 1992]. Cady et al. reported that the mean maximum diameter of breast cancers upon diagnosis declined by 10% every 5 years and from about 3 cm to about 2 cm from 1968 to 1988 [Cady 1997]. In the five years from 1989 through 1993, the median maximum diameter of all invasive breast cancers was only 1.5 cm at diagnosis. This decrease in size has been seen in numerous other reports. These same authorities report a diminution in the number of patients who have axillary lymph node metastasis.

At the New England Deaconess Hospital, only 31% of all patients with invasive breast cancer were found to have involved lymph nodes at diagnosis. In addition, over 40% in that series had only one lymph node involved and almost 50% had only micrometastases. While Cady has used this diminution in the incidence of lymph node metastasis to support the concept that no ALND is necessary for the management of women with mammographically detected T1a or T1b breast cancer [Cady 1994], these findings can be used equally well to support the fact that in a large percentage of women, removal of the SN alone may result in not only accurate staging, but in effective regional control. Giuliano's studies have shown that in approximately 70% of the cases, the SN is the only involved node in patients with early breast cancer. Albertini et al. has seen similar results; noting that the SN was the only involved node in at least 50% of cases [Albertini 1996]. It is quite possible that after accurate staging with SLND, no residual tumor is left in the remainder of the non-sentinel axillary lymph nodes, and regional control will be accomplished. However, it also may be that some women with SN metastases will have micro-or macrometastases in non-SN that will progress and develop into regional recurrences that may or may not be associated with a diminution of overall survival. In addition, it is possible that metastases in non-SN would be destroyed or inhibited by the adjuvant systemic therapy that is given to most women with involved lymph nodes. In addition, some metastases may be ablated by opposing tangential fields of radiation therapy.

In addition, it is quite possible that lymph node metastases are indeed "indicators but not governors" of distant metastases [Cady 1984]. This concept can be supported by the observations that variations in loco-regional management including the elimination of ALND (as in B04) have not generally been associated with alterations in overall survival (with some exceptions). Additional experimental works by Nicholson and Dulski [Nicholson 1986] and Brodt et al. [Brodt 1990, Brodt 1991] have shown the site-specific metastatic potential of malignant cells. Axillary lymph node metastases may be site specific. Should metastases develop in the

axilla, delayed dissection may be as effective as immediate dissection on overall survival for these patients.

Although some studies do suggest an improvement in overall survival based on local control, it is not clear that axillary control is the ultimate link for these successes. The recent RT studies are the most compelling survival evidence, but they do not address breast conservation and include only premenopausal women [Ragaz 1997, Overgaard 1997]. This study will include both pre- and postmenopausal women with stage I and II disease.

1.1.6 The Design of Z0011

SLND offers the unique opportunity to examine the impact of ALND on regional control and survival in early stage disease. By performing a SLND, patients with regional metastasis can be identified. It is these patients, if any, who are likely to benefit from ALND. If there is a benefit to be achieved from ALND, it will not be in node-negative women. These women can therefore be spared the morbidity of ALND. The lower morbidity of SLND is obvious; however, to formally document this, patients will be evaluated by range of motion exams and arm measurements. All operative complications will be recorded.

If there were no outcome difference between these two arms, then the treatment with the least morbidity, presumably SLND, would be preferable. By randomly assigning SN positive women to axillary therapy consisting of at least a level I and II A LND or to no further axillary therapy, the impact of axillary lymphatic clearance on survival can be assessed. It may be that after removing a positive SN, no further surgery is necessary for the woman with regional lymph node metastases from early breast cancer. If axillary surgery is merely a staging (diagnostic) procedure, then no adverse effects should be seen when it is omitted and replaced by SLND.

1.2 Objectives

The primary objectives are:

Long term: To assess whether overall survival for patients randomized to Arm 2 (no immediate ALND) is essentially equivalent to (or better than) than that for patients assigned to Arm 1 (completion ALND).

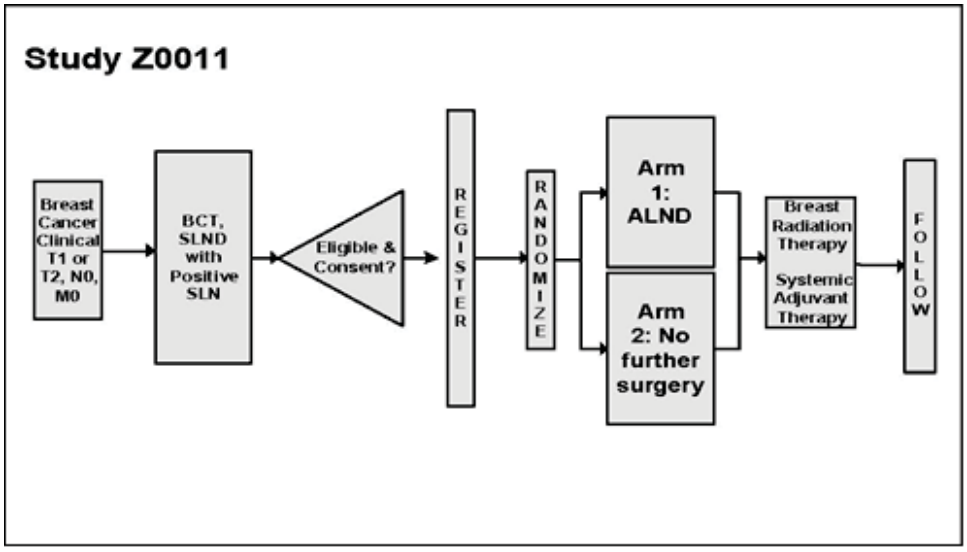
Short term: To quantify and compare the surgical morbidities associated with SLND plus ALND versus SLND alone.

1.3 Study Design

1.3.1 Accrual Goal

This study requires the randomization of 1900 evaluable patients over a period of 3.8 years based on a projected accrual rate of 500 eligible patients randomized per year. The randomization between the arms will be 1:1. The final analysis is projected for 8.8 years following the start of accrual.

1.4 Schema



2 Patient Selection

Each inclusion and exclusion criterion must be evaluated and **documented** in the patient's medical record. Patient eligibility must be determined by the investigator.

2.1 Inclusion Criteria

A patient will be eligible for inclusion in this study only if ALL of the following criteria apply:

PLEASE NOTE: Patients registered to this study may undergo intra-operative or postoperative randomization.

An investigator registering patients to this study **after completion of SLND (post-operative randomization)** is responsible for documenting that all of the eligibility requirements are met even if the SLND was not performed by the investigator.

1. Patient must be female.
2. Patient must be at least 18 years of age.
3. Patient's clinical stage must be documented as tumor size less than 5 cm, with no palpable nodes and no evidence of metastatic disease (T1 or T2 N0 M0; see appendices for staging criteria) and the tumor documented as amenable to lumpectomy.
4. Patient must have a tissue diagnosis of invasive breast carcinoma. **Note:** A patient can be registered to this study if they have a cytologic diagnosis suggestive of carcinoma from a fine needle aspiration (FNA) of a palpable or non-palpable breast lesion and the investigator believes the breast lesion is clinically suspicious for invasive breast carcinoma.
5. Date of the patient's first tissue diagnosis of invasive breast carcinoma or cytologic diagnosis of carcinoma must be no more than 60 days prior to the SLND.
6. The patient who had BCT (segmental mastectomy) performed previously, and is now referred to the local investigator for SLND, is eligible if the BCT was less than or equal to 60 days prior to the SLND. **NOTE**: Copies of the operative and pathology reports must be submitted as part of the registration process.
7. Patient must have ECOG/Zubrod status =2, as documented in patient's medical record.
8. Patient must be available for follow-up.
9. Patient of childbearing potential must have a negative serum or urine pregnancy test within 14 days of beginning study interventions.
10. Patient must have access to radiation therapy.
11. A sentinel lymph node must be identified that contains metastatic breast cancer as documented by frozen section, touch prep, or H&E staining on permanent section. (Refer to the Staging Criteria section in the protocol.) **NOTE:** Patients with metastatic breast cancer identified by immunohistochemistry (IHC) are not eligible.
12. Patient randomized to ALND must undergo ALND within 42 days of their SLND.
13. A patient with a history of a previous malignancy is eligible for this study as long as the patient meets the following criteria for a cancer survivor. A cancer survivor is eligible provided that the following criteria are met:
    a. The patient has undergone potentially curative therapy for all prior malignancies,
    b. There has been no evidence of any prior malignancies for at least five years with no evidence of recurrence (except for effectively treated basal cell or squamous carcinoma of the skin, carcinoma in -situ of the cervix that has been effectively treated by surgery alone, or lobular carcinoma in-situ of the ipsilateral or contralateral breast treated by surgery alone), and
    c. The patient is deemed by their treating physician to be at low risk for recurrence from prior malignancies.
14. Patient or the patient's legally acceptable representative must provide a signed and dated written informed consent prior to registration and any study-related procedures.
15. Patient must provide written authorization to allow the use and disclosure of their protected health

information. **NOTE:** This may be obtained in either the study-specific informed consent or in a separate authorization form and must be obtained from the patient prior to study registration.

2.2 Exclusion Criteria

A patient will be ineligible for inclusion in this study if ANY of the following criteria apply:

1. Patient is lactating (breastfeeding).
2. Patient has been previously treated with chemotherapy, estrogen receptor antagonists (i.e., Tamoxifen) or selective estrogen receptor modulators (SERMs, i.e., Raloxifene) for this invasive breast cancer.
3. Patient has a previously placed pre-pectoral breast implant. **NOTE:** A subpectoral implant is allowed.
4. Patient has concurrent invasive bilateral breast malignancies.
5. Patient has clinically and radiologically identified multi-centric disease that is not amenable to a single lumpectomy .
6. Patient has had previous ipsilateral axillary surgery such as excisional biopsy of lymph node(s), treatment of hidradenitis.
7. Patient has a medical contraindication to ALND or is considered a poor surgical risk due to a non-malignant systemic disease (cardiovascular, renal, etc.) that would preclude the treatment options.
8. Patient who is noted to have matted nodes or gross extranodal disease at the time of SLND.
9. Patient has three or more positive sentinel nodes by frozen section, touch prep, or H&E staining on permanent section.

2.3 Staging Criteria

For this study, patients will be staged according to the AJCC Cancer Staging Manual, 5th edition, 1997 (See Appendix for *Staging Reference).* NOTE: In the 5th edition, specific criteria for micrometastatic lymph node deposits are not defined. Although the 6th edition of the AJCC Cancer staging manual defines micrometastases as tumor deposits greater than 0.2mm but not greater than 2.0mm in largest dimension, this definition is not used to determine eligibility for Z0011. Therefore, for this study, a SLN with a micrometastatic tumor deposit < 0.2mm will also be considered a positive SLN.

3 Study Calendar

Timing * (From date of last operation)	Intervention or Procedure
Within 14 days prior to study intervention	Disease assessment Assessment of axillary bed and arm effects
Post-operative registration and randomization	
Within 42 days of ALND (Arm 1)	Segmental Mastectomy and sentinel lymph node dissection (SLND)
Registration	Document eligibility criteria and informed consent
Intervention Day	Arm 1: ALND Arm 2: No additional surgery
Adjuvant Treatment	Whole breast radiation therapy
	Adjuvant systemic therapy, if indicated
Pre-registration with intra-operative randomization	
Pre-registration	Document eligibility criteria and informed consent
Intervention Day	Segmental mastectomy and sentinel lymph node dissection (SLND)
	Randomization to study arm
	Arm 1: ALND Arm 2: No additional surgery
Adjuvant Treatment	Whole breast radiation therapy
	Adjuvant systemic therapy, if indicated
FOLLOW UP	
Day 30	Assessment of side effects related to surgical intervention Complications since the last visit
Day 90 (Optional visit; according to patient's clinical needs)	Assessment of side effects related to surgical intervention, including axillary bed and arm effects Complications since last visit
Month 6, 12	Assessment during or after completion of adjuvant treatment Assessment of long term surgical side effects, including axillary bed and arm effects Disease assessment for recurrence or other cancers
Month 18	Assessment during or after completion of adjuvant treatment Assessment of long-term surgical side effects Disease assessment for recurrence or other cancers
Month 30	Assessment of long-term surgical side effects Disease assessment for recurrence or other cancers
Month 36, and then yearly until 10 years	Disease assessment for recurrence or other cancers

* If the patient's next follow-up visit occurs in advance of or later than the time specified for the next scheduled visit, note the actual visit date on each CRF.

4 Registration/Randomization

There are two options for registering and randomizing a patient to Z0011.

1. **Post-Operative Registration with Randomization** must be followed when the patient is eligible for this study following completion of SLND and confirmation of metastatic breast cancer in a sentinel node by H&E staining on permanent section.
2. **Pre-Registration with Intra-Operative Randomization** can be used for sites electing to randomize intra-operatively based on frozen section or touch prep assessment of sentinel node status.

4.1 ACOSOG Companion Study Z0010

This section applies to clinical sites that have both ACOSOG Study Z0010 and Study Z0011 open. ACOSOG Study Z0010 is designed to assess the prognostic significance of occult metastases detected by IHC in sentinel lymph nodes that are negative by hematoxylin and eosin (H&E) staining in women with early-stage breast cancer. It also is designed to assess the prognostic significance of occult metastases detected in the bone marrow by immunocytochemistry (ICC) in this patient group.

The accrual goal for ACOSOG Study Z0010 was met and the study was permanently closed to accrual on 5/30/2003. All patients currently on the study must continue to be followed according to protocol specifications. Annual IRB review and approval of the protocol and consent form must continue until all registered patients have completed the follow-up phase of the study.

4.2 Randomization Arms

Women with clinical stage T1 or T2 N0 M0 breast cancer who are found to have a SN containing metastatic breast cancer through SLND with BCT, as documented on frozen section, touch prep, or permanent section evaluation by H&E staining, will be randomized to one of two Arms:

Arm 1: Completion ALND, followed by whole breast radiation therapy and, if indicated, systemic adjuvant therapy

OR

Arm 2: No immediate additional axillary surgery or axillary-specific radiation, followed by whole breast radiation therapy and, if indicated, systemic adjuvant therapy.

4.2.1 Assessment of Stratification Factors

The following factors are believed to be prognostic for survival and will be used in the randomization as dynamically balancing stratification factors:

- Age: ≤50 or > 50.
- Estrogen Receptor (ER) status: positive or negative.
- Tumor size: ≤ 1 cm, > 1 cm or ≤ 2cm, or >2 cm.

4.3 Registration/Randomization Procedures

Registration is available 24 hours a day by accessing the ACOSOG web site at http://www.acosog.org. ACOSOG staff is accessible at the ACOSOG Coordinating Center on Monday through Friday, from 8:00 AM to 5:00 PM Eastern time. For detailed registration guidelines, refer to the Patient Registration SOP on the ACOSOG web site.

4.3.1 Registration Worksheet

The Registration Worksheet of the CRF (RW CRF) must be completed as documented in the patient's medical record **PRIOR** to initiating the registration procedure for either preregistration with intra-operative randomization or for post-operative registration/randomization. A completed worksheet must be submitted within 24 hours of the registration.

To be eligible for registration to this study, the patient must meet each inclusion and exclusion criterion listed on the eligibility checklist. There is no mechanism for making exceptions to the eligibility requirements.

4.3.2 Pre-Registration with Intra-operative Randomization

Pre-registration is available 24 hours a day by accessing the ACOSOG web site at http://www.acosog.org. ACOSOG staff is accessible at the ACOSOG Coordinating Center on Monday through Friday, from 8:00 AM to 5:00 PM Eastern time. For detailed registration guidelines, see the Standard Operating Procedure Patient Registration (PatReg SOP) on the ACOSOG web site.

Pre-registration is necessary in advance of intra-operative randomization. The ACOSOG registration program performs a pre -registration and issues "tokens" for completion of the registration and randomization intra-operatively.

The pre-registration and intra-operative registration and randomization procedures are as follows:

1. Documented informed consent must be obtained prior to the pre-registration process.
2. RW CRF must be completed prior to patient pre-registration. No exemptions or waivers will be granted for patients who do not meet the eligibility criteria.
3. The pre-registration process consists of accessing the ACOSOG website (http://www.acosog.org) and (a) confirmation of the validity of investigator membership, Institutional Review Board (IRB) approval, skills, etc., (b) assignment and recording of the ACOSOG Patient Identification Number, and (c) assignment and recording of the token (a randomly generated 8-digit number linked to the patient information submitted).
4. Confirmation of pre-registration is e-mailed from the ACOSOG Coordinating Center to the clinical site immediately following the pre-registration.
5. During surgery, use a touch-tone telephone to access the automated Interactive Voice Response (IVR) system for randomization by calling 866 488 0651 or 919 668 7126. The person placing the randomization call responds to pre-recorded voice requests using the touch-tone pad. The caller will be prompted to provide the token given during the preregistration process. Once the token is verified, the randomized treatment Arm is given.
6. Submission of the completed RW CRF is required within 24 hours following completion of patient registration. The RW CRF must be faxed to 919 668 8466, the DataFax system at the ACOSOG Coordinating Center.

If a patient's SN is found to be negative by frozen section, the site has the option of canceling the token at this point. The site also may opt to defer token cancellation until after final pathology has confirmed a negative SN by H&E, since H&E may come back with a positive SN result. In this case, the uncancelled token may then be used by the site to obtain randomization.

If a patient is found to be ineligible during surgery for any other reason, cancel the token using the Cancel Token procedure on the Patient Registration page of the ACOSOG web site.

In the event of electronic or communication problems, see the Standard Operating Procedure Patient Registration (PatReg SOP) on the ACOSOG web site for emergency procedures. All sites should have a printed copy of this SOP available for reference.

4.3.3 Post-Operative Registration with Randomization

Registration is available 24 hours a day by accessing the ACOSOG web site at http://www.acosog.org. ACOSOG staff is accessible at the ACOSOG Coordinating Center on Monday through Friday, from 8:00 AM to 5:00 PM Eastern time. For detailed registration guidelines, see the Standard Operating Procedure Patient Registration (PatReg SOP) on the ACOSOG web site.

The registration and randomization procedures are as follows:

1. Documented informed consent must be obtained prior to any study related procedures or assessment being conducted.
2. Prior to registration, the RW CRF must be completed. No exceptions will be granted for patients who do not meet the eligibility criteria.
3. The registration and randomization process consists of accessing the ACOSOG website (http://www.acosog.org) and (a) confirming the validity of the investigator membership, IRB approval, etc., (b) assigning and recording an ACOSOG Patient Identification Number, and (c) assigning and recording a treatment Arm and any other applicable data requested on the RW CRF for that patient.
4. Confirmation of the registration is e-mailed from the ACOSOG Coordinating Center to the clinical site immediately following the registration.
5. Within 24 hours following registration, the completed RW CRF should be faxed to 919 668 8466, the DataFax system at the ACOSOG Coordinating Center.

In the event of electronic or communication problems or other emergencies, see the Standard Operating Procedure Patient Registration (PatReg SOP) on the ACOSOG web site. All sites should have a printed copy of this SOP available for reference.

4.3.4 North Central Cancer Treatment Group (NCCTG) Registration Instructions

A signed HHS 310 form must be on file at the NCCTG Randomization Center before patient entry.

NCCTG institutions must fax (507-284-0885) a completed ACOSOG Registration Worksheet 8 a.m. to 3:30 p.m. central standard time Monday through Friday to register a patient. Patient eligibility and existence of a signed consent form will be checked by the NCCTG Randomization Center before a patient will be registered into this study.

Upon confirmation of eligibility, the NCCTG Randomization Center will access ACOSOG's web-based registration system to register the patient. Eligibility information given in the Registration Worksheet will determine the type of registration that will be conducted by the NCCTG Randomization Center. ACOSOG Coordinating Center will e-mail the NCCTG Randomization Center (jacobson.susan2@mayo.edu, mahon.carol@mayo.edu, parkin.diane@mayo.edu) a confirmation of registration that will include the following:

- ACOSOG Patient ID Number
- Patient randomization (if **web-based registration and randomization** was conducted), **OR**
- 8-digit token number (if **web-based pre-registration** was conducted) Note: randomization will NOT be given at this point.

This information will be forwarded to the registering institution by the NCCTG Randomization Center.

To obtain patient randomization if pre-registration was performed, refer to Section 4.3.2 (Pre-Registration with Intra-operative Randomization) and follow the steps starting from #5. If the patient is found ineligible for the study after pre-registration (i.e. patient did not have positive sentinel node), the institution will cancel the token (see Section 4.3.2).

All investigators must be registered with CTEP, DCTD by the annual submission of the FDA Form 1572 and a current CV. To obtain an NCI/CTEP investigator number, investigators should complete and submit (by USMail or Express Courier, faxes are not acceptable) an FDA Form 1572, with an original signature, and a current curriculum vitae to the PMB (Pharmaceutical Management Branch):
Pharmaceutical Management Branch, CTEP, DCTD, NCI 6130 Executive Boulevard, Room 7149 Rockville, MD 20852 Phone: 301-496-5725

A copy of this submission must be sent to the NCCTG Operations Office.

The FDA Form 1572, with instructions, is available on the NCI home page (http://ctep.info.nih.gov) or by calling the PMB at 301-496-5725.

NCCTG Adverse Event (AE) Monitoring and Reporting – Report according to ACOSOG guidelines.

NCCTG Data Considerations – Report according to ACOSOG guidelines.

5 Interventions

This section gives an overview of the intervention(s) and procedures to be used in this study and how they are to be applied. Specific interventions and procedures are identified in bold italics. The details of the interventions and procedures associated with this protocol are described in the *Details of Intervention and Procedures* section of this protocol.

5.1 Intervention Scheme

A patient will be eligible for this trial only if metastatic tumor is detected in the SN by routine ***histopathology***, either on frozen section, touch prep, or permanent sections.

The patient will be randomized to one of two Arms, Arm 1 or Arm 2, where the interventions associated with these Arms are as follows:

> **Arm 1:** Level I and II ***Axillary lymph node dissection (ALND)*** followed by adjuvant ***breast radiation therapy*** and, if indicated, ***adjuvant systemic therapy***.
>
> **Arm 2:** ***Breast radiation therapy*** and, if indicated, ***adjuvant systemic therapy*** only (no immediate further axillary-specific interventions).

There are two procedural options for implementing the ALND in patients randomized to Arm 1 depending on the option used to register the patient:

1. **Post-Operative Registration with Randomization.** Obtain the informed consent and randomize the patient postoperatively only if the SN demonstrates metastatic disease and the patient is otherwise eligible. If the patient is randomized to Arm 1, then the ALND is performed as a second operation. If the patient is randomized to Arm 2, then a second operation should not be performed.
2. **Pre-Registration with Intra-Operative Randomization.** Use frozen section or touch prep assessment of the SN to ascertain eligibility during surgery and randomize intraoperatively if the node is positive. If the patient is randomized to Arm 1, proceed immediately with an ALND. If the patient is randomized to Arm 2, then an ALND should not be performed.

All patients, regardless of when they are randomized and which arm they are assigned to, should be treated with whole ***breast radiation therapy*** and, if indicated, ***adjuvant systemic therapy.***

The ***ALND*** (to be done as a result of being randomized to Arm 1), ***breast radiation therapy***, and ***adjuvant systemic therapy*** should be performed as defined.

5.2 Details of Intervention and Procedures

5.2.1 Segmental Mastectomy (Lumpectomy)

All patients will undergo resection of the segment of breast tissue, which contains the primary breast tumor with a clear margin of removed normal tissue around the periphery of the tumor. In addition, the underlying pectoral fascia, but not the pectoralis major muscle, together with a segment of overlying skin, may be removed if deemed necessary. The specimens will be oriented for histopathologic examination. The specimens may be inked by the surgeon. Margins must be assessed and deemed tumor free by the institutional pathologist. Copies of the institution's operative and pathology reports must be submitted to the ACOSOG Coordinating Center.

5.2.2 *Lymphoscintigraphy/ Intraoperative Gamma Counting*

For patients with medial hemisphere lesions, defined as a tumor that is completely medial to the border of the areola, either a lymphoscintigram or report of intraoperative gamma counting is required. A copy of the nuclear radiologist's report must be submitted in cases with a lymphoscintigram, and a copy of the operative gamma counting must be submitted with the operative report.

5.2.3 Sentinel Lymph Node Dissection (SLND)

SLND may be performed with isosulfan blue dye, a radiopharmaceutical, or a combination of both. Regardless of the technique utilized, a lymphoscintigram or intra-operative gamma counting must be performed on all patients with medial hemisphere breast tumors to ensure that the primary drainage pathway is to the ipsilateral axilla. For the purpose of this protocol, a medial hemisphere lesion is defined as one in which the entire tumor is medial to the most medial margin of the areola. Patients who do not have

drainage to the ipsilateral axilla will be excluded from the study. When a lymphoscintigram is obtained, a copy of the nuclear medicine physician's lymphoscintigram report must be submitted. Since only one of several different methods will be used for identifying the SN, each investigator should determine the technique, which represents the best practice at his/her institution.

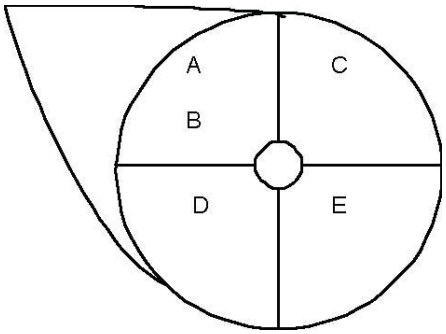
Although this study does not dictate which technique should be used, guidelines are provided here for the various techniques. Regardless of the technique used, no more than four gross SNs should be removed in each patient. If a surgeon is removing more than four nodes on a repeated basis, the surgeon will be subject to a performance audit. At times, the pathologist may identify more lymph nodes than the surgeon did. Therefore, the final number of SNs may exceed four, and this will not reflect on surgeon performance.

Blue Dye Technique

The following method may be utilized for this procedure:

After the induction of general anesthesia or local anesthesia with heavy intravenous sedation and prepping and draping of the patient, 4-5 cc of 1% isosulfan blue dye is injected into the breast parenchyma surrounding the primary tumor, or into the wall of the cavity created by the previous biopsy. If the lesion is not palpable, a mammographic or ultrasonographic localization will be required. A needle may be left in the breast parenchyma through which the blue dye can be instilled in the operating room. The breast is gently compressed to augment the action of the lymphatic pump and promote passage of blue dye to the axilla. The timing of the axillary incision after the injection of the blue dye and the volume of dye injected are extremely important and dependent upon the location of the primary tumor. Suggestions for volume of injectate and timing are given below.

After the allotted time, a transverse incision is made just inferior to the hair-bearing region of the axilla. Blunt dissection is then carefully performed with the tips of a curved hemostat to identify a blue-stained lymphatic channel located just below the superficial axillary fascia. It is helpful to raise the arm above the patient's head (≈135° abduction) to facilitate the identification of the blue lymphatic channel. Do not raise skin flaps. The blue lymphatic channel is followed proximally and distally until the first blue node or SN is identified. The SN may be sent to pathology for frozen section. Depending on the histology of the SN, the patient will be treated accordingly.



Location of Primary Tumor	Suggested Volume of Dye to Inject	Suggested Time from Injection to incision
A. High Upper Outer Quadrant Lesions	4 cc	3-4 minutes
B. Lower Upper Outer Quadrant Lesions	4-5 cc	5 minutes
C. Upper Inner Quadrant Lesions	4-5 cc	5 minutes
D. Low Outer Quadrant Lesions	5 cc	5 minutes
E. Low Inner Quadrant Lesions	5 cc	7 minutes

Radiolabeled Sulfur Colloid Technique (Hot Technique)

Prior to the operation, 0.25mC to 1.0 mC of radiolabeled technetium sulfur colloid will be injected into the breast parenchyma surrounding the primary tumor or into the wall of the cavity created by the previous biopsy. If the lesion is non-palpable, a mammographic or ultrasonographic localization will be required. A needle may be left in the breast parenchyma through which the radioactive colloid may be instilled. Care should be made not to contaminate the skin with the radiopharmaceutical. After the induction of general

anesthesia or heavy intravenous sedation, a gamma counter will be used to localize the SN. For patients with inner hemisphere lesions, the surgeon must identify axillary drainage. Each gamma counter should be calibrated according to the manufacture's recommendations. For example:

C Trak→, Carewise Medical, Palo Alto, California: initial settings should be a window of 30KeV and a threshold of 130KeV. To optimize weak signals the window may be increased to 40KeV and the threshold decreased to 120KeV.

Neoprobe→, Dublin, Ohio: initial settings should be a threshold of 120KeV and a window of 40KeV. Some adjustments may be made using the squelching options.

Navigatorρ, USSC, Norwalk, Conn: Initial settings should be a threshold of 90-100KeV. Pitch and count time may be adjusted.

A sterile plastic sheath should be used to cover the probe. The lymphatic drainage pattern is mapped in the operating room and a transverse incision is made over the axillary "hot spot."

Dissection is then carefully performed until the signal intensifies and an axillary lymph node is found. Once the SN is identified and removed, the axillary basin should be measured for any residual radioactivity. If the basin remains "hot", an attempt should be made to find a second SN. If the SN is not identified secondary to the "shine through" from the primary injection site then the segmental mastectomy may be performed prior to the sentinel lymph node biopsy. The SN may be sent to pathology for frozen section if allowed by the institution's radiation safety officer. If a frozen section or touch prep is not permitted then the treatment must be based on the permanent section diagnosis.

Combined Blue and Hot Technique

Prior to the operation, 0.25 mC to 1.0 mC of a radiolabeled technetium sulfur colloid will be injected into the breast parenchyma surrounding the primary tumor or into the wall of the cavity created by the previous biopsy. If the lesion is non palpable, a mammographic or ultrasonographic localization will be required. A needle may be left in the breast parenchyma through which the radioactive colloid and the blue dye may be instilled. After the induction of general anesthesia or heavy intravenous sedation, prepping and draping the patient, 4-5 cc of isosulfan blue dye will be injected as previously described. The breast is then gently compressed to augment the action of the lymphatic pump and promote passage of blue dye to the axilla. During the delay from injection to axillary incision the gamma probe (either C Trak→, Neoprobe→ or Navigatorρ) may be used to map the lymphatic drainage pattern.

After 3-7 minutes, a transverse incision is made just inferior to the hair-bearing region of the axilla. Blunt dissection is then performed to identify a blue stained lymphatic channel. The blue lymphatic channel is then followed proximally and distally until the first or SN is identified. This can be confirmed with the gamma counter. If the SN is not identified with the blue dye and the "shine through" from the primary site interferes with the ability to identify the "hot spot," the lumpectomy may be performed prior to identifying the SN. However, removal of the tumor prior to injection of the blue dye is discouraged. Once the SN has been removed, the axillary basin should be measured for any residual radioactivity. If the basin remains "hot" then an attempt should be made to find a second SN. The SN may be sent to pathology for frozen section or touch prep may be done if allowed by the individual institution's radiation safety officer. If a frozen section or touch prep is not permitted then the treatment must be based on the permanent section diagnosis.

5.2.4 Axillary Lymph Node Dissection (ALND) for Arm 1

Patients will undergo removal of at least level I and II axillary lymph nodes. If necessary, the pectoralis minor muscle may be incised but not removed. At least ten lymph nodes should be identified in the axillary specimen. If ten lymph nodes are not identified, then the patient will still be included in the study. Surgeons who consistently remove less than 10 axillary lymph nodes will be re-evaluated for continued inclusion in this study. Copies of the operative and pathology reports must be forwarded to the ACOSOG Coordinating Center.

5.2.5 Adjuvant Radiation Therapy (Arm 1 & 2)

All patients will undergo adjuvant radiation therapy. The breast radiation therapy to be done on this protocol specifically excludes adding a third (supraclavicular) field because that would confound the issue being addressed by the study. In addition, the breast radiation therapy given is subject to review. A sample of patients will be selected and the clinical sites will be required to submit the portal films for those patients to a central review. The portal films, prescriptions, and supporting physics documentation for randomly selected

patients will be requested and therefore the clinical site is advised to prepare to the extent possible for such requests.

Dose: Dose to the prescription point for the breast is 45 Gy to 50 Gy, in equal daily fraction sizes of 1.8 to 2.0 Gy per day, 5 days per week. For whole breast doses below 50 Gy, a boost dose must be prescribed to bring the primary surgical tumor bed to a minimum total dose of 50 Gy. Higher doses to the boost volume may be given at the discretion of the radiation oncologist.

Dose Specifications: The dose will be prescribed to the entire breast volume or clinical target volume (CTV). The CTV will be defined with the patient in the supine treatment position by palpating the periphery of the breast tissue and marking it with radio-opaque markers, such as lead wire. In a patient with surgical clips placed in the tumor bed, the clips must be within the CTV. The planning target volume (PTV) is the clinical target volume plus a margin of 1.0 to 2.0 cm superiorly, inferiorly, medially, and laterally. Tangent fields with a coplanar posterior border are used. The prescription point used is the lung-chest wall interface in the central axis plane. This prescription method ensures that the entire PTV receives a minimum dose equal to the prescription dose. The dose to this point, as well as the maximum dose to the PTV or the central axis plane should be reported. Inhomogeneity corrections are not allowed.

Technical Factors

- Equipment must have nominal photon energies between 4 MV and 8 MV.
- Compensators, wedges, or dynamic therapy must be used to keep the maximum PTV dose within 15% of the prescription.
- The beam may be shaped, with a margin, to the shape of the breast with cerrobendtype blocking or by using a multi-leaf collimator.
- Fields will be designed using a simulator unit or CT simulator with appropriate patient immo bilization for daily accuracy. Use of an Alpha-cradle would be one example. A mammorex board is another.

Critical Structure Dose

The maximum distance from the posterior or deep field border to the lung/chest wall interface will be 3.0 cm, anywhere in the field.

Treatment Interruptions

If a treatment interruption is necessary for acute radiation toxicity of the skin, aggressive treatment of the area with a product like Duodermρ is encouraged to minimize the treatment break. The total time to deliver the radiation therapy should not exceed 8 weeks.

Supraclavicular Field

The use of a third field to cover the supraclavicular area is not allowed.

Side Effects

Fatigue is the anticipated systemic reaction to radiation. Skin erythema and desquamation also may occur. Breast edema, tenderness, and myositis also are acute side effects. Possible long-term complications include radiation pneumonitis, rib fractures, and cardiac complications for left-sided lesions.

5.2.6 Adjuvant Systemic Therapy (Arm 1 & 2)

The use of systemic adjuvant therapy is advised for the node-positive women. The type of systemic therapy offered is at the discretion of the treating physician and the patient. The type of therapies discussed in the *Background* section of this protocol or enrollment onto another clinical trial is encouraged. When selecting another clinical trial as the means of administering systemic adjuvant therapy then special care should be used to avoid trials for which the collection of data needed for this trial would be compromised; in general, this should not be a major problem.

5.3 Study Withdrawal

Patients will be withdrawn from the study for the following reasons:

1. If a patient was registered to the study based on cytologic diagnosis suggestive of carcinoma from FNA of a palpable or non-palpable breast lesion, but the final tissue diagnosis does not demonstrate invasive breast carcinoma, the patient will be discontinued from the study and will not be followed.

2. A patient with tumors located in the medial hemisphere of the breast that show a complete absence of drainage to the axilla by lymphoscintigram or by absence of elevated axillary lymph node gamma counts will be discontinued from the study and will not be followed.
3. If the final pathology report identifies three or more positive sentinel nodes, the patient will be discontinued from the study and will not be followed.

6 Follow-up

6.1 Subsequent Care

All patients should be instructed to communicate with the investigator or study surgeon prior to consenting to additional therapy (not included in this protocol).

6.2 Disease-Related Assessments

Patients will be monitored for local and regional recurrence (especially recurrence in the ipsilateral axillary bed), contralateral breast primary tumors, distant recurrence, progression, and death. Patients also will be monitored for additional non-breast primaries, which should be confirmed histologically whenever possible.

6.2.1 Suggested Assessments in Response to Symptoms

The following assessments are recommended for the purposes of disease evaluation in the presence of symptoms:

- If patient has new symptoms of bone or back pain, a bone scan and relevant x-rays should be done.
- If patient has symptoms of abdominal pain, or the physician notes jaundice, hepatomegaly, or an elevation in the liver function tests, then a CT scan or MRI of the abdomen should be obtained.

If patient exhibits a change in mental or neurologic status, then a CT scan or MRI of the brain should be obtained.

6.3 Assessment of Axillary Bed and Arm Effects

Special assessments for surgical side effects in the axillary bed and arms will be as required by the Study Calendar. These assessments will be done on all patients, regardless of whether an ALND was done. The Follow-up Breast and Arm Assessment case report form (FBAA CRF) will be used. This form is specially designed for the following assessments:

- Axillary pain or numbness.
- Range of motion limitations noted on abduction.
- Ipsilateral edema of the arm as demonstrated by an increase that is > 10% in circumference of the affected arm from the pre-operative measurement. Symptoms of lymphedema also should be noted.

7 Evaluation of Outcomes

The primary endpoint is overall survival. Overall survival is defined as the time from the date of initial diagnosis until the date of death. Patients will be followed for overall survival for a maximum of 10 years from the date of surgery. Secondary endpoints of interest are:

1. Distant disease-free survival. Distant disease is defined as the distant recurrence of breast cancer. Breast cancer in the contralateral breast or ipsilateral axilla is not a distant recurrence.
2. Comparison of surgical morbidities associated with SLND plus ALND versus SLND alone.

8 Adverse Event Reporting

8.1 Definition of Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a patient that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

8.2 Definition of Serious Adverse Event

A **Serious Adverse Event (SAE)** is defined as any untoward medical occurrence that:

- Results in death or
- Is life-threatening (at the time of the event) or
- Requires inpatient hospitalization or prolongation of an existing hospitalization or
- Results in persistent or significant disability or incapacity or
- Is a congenital anomaly/birth defect (in an offspring).

Medical and scientific judgment should be exercised in deciding whether the designation of an event as serious, is appropriate in other situations, such as medical events that may not be immediately life threatening but may require intervention to prevent one of the outcomes listed above.

8.3 NCI Common Toxicity Criteria

This study will collect AEs using the current version of the NCI Common Toxicity Criteria (CTC), if applicable. An electronic version of the CTC may be accessed through the web at http://ctep.cancer.gov/. The CTC provides a descriptive terminology that is to be used for AE reporting. A grading (severity) scale is also provided in the CTC for each AE term.

8.4 Expected Adverse Events

8.4.1 Short-Term Effects

Short-Term Effects are specific surgically-related events expected during this study that are to be followed using the Short-Term Surgical Effects case report form (SSE-CRF). The SSE-CRF will be used to report the status of the patient's AEs during the 30-day period following the last study-related operation.

The following surgery-related events must be reported if the event(s) occur:

- Allergic reaction/hypersensitivity (to dye or radionucleotide that requires administration of histamine antagonists or systemic support)
- Wound infection (breast or axillary wound infection that results in the opening of the wound or administration of antibiotics non-prophylactically)
- Wound non-infection (axillary seroma that requires the opening of the wound or placement of a drain)
- Wound non-infection (axillary hematoma that requires surgical evacuation)
- Neuropathy-sensory (axillary paresthesia and/or intercostobrachial nerve paresthesia)
- Operative injury (brachial plexus injury)

8.4.2 Long-Term Effects

Long-Term Effects are specific surgically-related events expected during this study that are to be followed using the Long-Term Surgical Effects case report form (LSE-CRF). The LSE-CRF will be used to report the status of the patient's AEs assessed as required by the Study Calendar.

The following surgery-related events must be reported if the event(s) occurs, continues, or progresses:

- Lymphatics (lymphedema -- arm circumference 2 cm greater or more than baseline measurement)

- Neuropathy-sensory (axillary paresthesia)
- Operative injury (brachial plexus injury)

8.4.3 Reporting of Expected Adverse Events

AEs that are expected and listed as short term or long-term effects will be reported using the appropriate CRFs, SSE-CRF or LSE-CRF.

Expected AEs related to radiation therapy or adjuvant systemic therapy are not listed as part of this protocol. Any AEs noted as expected by other sources that are Grade 1,2, 3 or 4 should not be reported.

Expedited reporting is required for any expected AE that is reported as fatal (Grade 5) within 30 days following the study intervention regardless of attribution.

All reported AEs should be followed until final resolution.

8.5 Unexpected Adverse Events

An Unexpected Adverse Event is any event that is not listed as a short-term or long-term effect in the *Expected Adverse Events* section of this protocol.

8.5.1 Reporting of Unexpected Adverse Events

All unexpected AEs **related to surgical interventions** will be reported using the AE-CRF. The severity of the event should be graded using the CTC criteria, if applicable or if the grade categories are listed under "Grade of Adverse Event" in the section below. Attribution also should be determined and reported on the CRF. Categories of attribution are defined under "Attribution of Adverse Event" in the section below."

Exception: Unexpected AEs related to radiation therapy or adjuvant chemotherapy that are Grade 1, 2, or 3 should not be reported.

Expedited reporting is required for any unexpected AE that is reported as life threatening (Grade 4) or fatal (Grade 5) that occurs within 30 days following the study intervention regardless of attribution.

All reported AEs should be followed until final resolution.

8.5.2 Attribution of Adverse Event

Attribution must be determined by the investigator or study surgeon, documented and reported. The following categories should be used when determining whether an AE is related to the medical treatment or surgical procedure:

Definite	Clearly related to medical treatment or surgical procedure
Probable	Likely related to medical treatment or surgical procedure
Possible	May be related to medical treatment or surgical procedure
Unlikely	Doubtfully related to medical treatment or surgical procedure
Unrelated	Clearly NOT related to medical treatment or surgical procedure

8.5.3 Grade of Adverse Event

The severity of each event should be graded using the CTC criteria, if applicable. If the event is not in the CTC, the following categories should be used when determining the severity of an AE:

0	No adverse event or within normal limits
1	Mild adverse event
2	Moderate adverse event
3	Severe adverse event
4	Life -threatening adverse event
5	Fatal adverse event

8.6 Expedited Adverse Event Reporting

An expedited adverse event report requires submission to ACOSOG. The new Word version of the AdEERS form is available on the ACOSOG web site at www.acosog.org. This Word document can be downloaded, completed, and emailed to ACOSOG at AdEERS@surgerytrials.duke.edu .The ACOSOG will fax the form to the NCI upon receipt.

Failure to report AEs in a timely manner may result in suspension of the investigator. AE reporting is in addition to and does not supplant the reporting of adverse events as part of the data submission requirements for the study.

8.6.1 What to report:

Summary of Expedited Reporting of Adverse Events for Surgical Procedures Only:

UNEXPECTED EVENT			EXPECTED EVENT		
Grades 1 – 3 Regardless of Attribution	**Grade 4 Regardless of Attribution**	**Grade 5 Regardless of Attribution**	**Grades 1 – 3 Regardless of Attribution**	**Grade 4 Regardless of Attribution**	**Grade 5 Regardless of Attribution**
Adverse Event Expedited Reporting NOT required.	Expedited report within 10 working days.	Report by phone to NCI and ACOSOG within 24 hrs. Expedited report to follow within 10 working days.	Adverse Event Expedited Reporting NOT required.	Adverse event expedited reporting NOT required.	Report by phone to NCI and ACOSOG within 24 hrs. Expedited report to follow within 10 working days.
All deaths within 30 days of the date of surgery regardless of attribution must be reported. Any late death (> 30 days of the date of surgery) attributed to study intervention (possible, probable or definite) should be reported within 10 working days.					

8.6.2 When to report

Once the investigative site **becomes aware of the event**, it should be reported within ten (10) working days. All fatal (Grade 5) adverse events should be reported by telephone to NCI and ACOSOG within 24 hours of the event.

8.6.3 How to report

Expedited adverse event reporting in NCI trials utilizes the AdEERS, "The Adverse Event Expedited Reporting System" An online AdEERS form cannot be used for surgical intervention only trials, such as Z0011 **DO NOT attempt to submit a completed form electronically through the AdEERS web site, as the system currently will not permit electronic submission of reports without the completion of Section 4, which requires a pharmaceutical agent.**

- Go to the ACOSOG web site at www.acosog.org.
- Click on the link for "Protocols and Adverse Event Links."
- Click on the link for "AdEERS for all other protocols."
- Save the Word form to a local computer and complete according to the instructions provided.
- E-mail the completed form as an attachment to AdEERS@surgerytrials.duke.edu .

The site is no longer required to fax a copy of the AdEERS form to the National Cancer Institute. The ACOSOG will fax the form to the NCI upon receipt.

8.6.4 Where to report:

ACOSOG: Microsoft Word form of AdEERS should be completed and submitted via email at AdEERS@surgerytrials.duke.edu - For paper submission: A copy of expedited adverse event reports can be sent to the ACOSOG Coordinating Center by fax at (919) 668-7156. All fatal (Grade 5) adverse events should be reported by telephone within 24 hours of the event. To make a telephone report, contact ACOSOG at (919) 668-8191, available 24 hours a day (recorder after hours from 5:00 PM to 9:00 AM EST).
Local IRB: All expedited adverse event reports should be sent to your local IRB. **NOTE**: Please consult your IRB for local reporting requirements.

9 Data Considerations

The clinical site should access the Z0011 protocol page of the ACOSOG web site, http://www.acosog.org to obtain full-size blank CRFs for data submission to the ACOSOG Statistics and Data Center.

Case Report Form Completion and Submission Guidelines

Effective November 14, 2011, all participating sites will submit patient data via fax to 507-293-3575 for entry by Statistics and Data Center personnel.

10 Statistical Considerations

This trial is designed to test the null hypothesis that survival for patients assigned to Arm 2 (no ALND) is significantly worse than for patients assigned to Arm 1 (ALND). Rejection of this null hypothesis would provide evidence in favor of clinical adaptation of SLND without ALND (Arm 2). A short-term primary objective is to quantify the morbidities associated with ALND and SLND.

The ACOSOG Data Monitoring Committee (DMC) will control access to and release of results from this study and closely monitor the study. The DMC will meet every six months and will be given a progress report at those meetings. Some of the progress reports will include scheduled formal analyses (see below).

The trial is planned with the intent of reporting results from short-term objectives following the completion of accrual to this randomized trial and prior to the time when results associated with the long-term objective (survival comparison) can be reported. The DMC will be asked for permission to report results associated with short-term objectives, with the overriding consideration being whether the release of these results could in any way compromise meeting the long-term objective.

The trial size is based on the requirements of the Z0011 primary long-term objective (testing the null hypothesis).

The following are trial size computations and use a type I error probability $\alpha = 0.05$ (one-tailed), and a type II error probability $\beta = 0.1$ (power=90%). These computations are done using a modification of the algorithm described by Rubinstein, Gail, and Santnor [Rubinstein 1981]. The primary analysis will be done using proportional hazard regression.

Let λ_A designate the hazard rate in Arm 1, and λ_B designate the hazard rate in Arm 2. The hypotheses are:

H_0: $\lambda_B/\lambda_A \geq \Phi$ against H_a: $\lambda_B/\lambda_A < \Phi$,

Where Φ specifies the hazard ratio criterion that indicates that the survival outcome in Arm 2 is worse than for Arm 1, H_0 is the null hypothesis and H_a is the alternative hypothesis. The specific criterion for inferiority of Arm 2 used in the computations is $\Phi = 1.3$, with equivalence in the hazard ratio ($\Phi = 1$) as the specific alternative hypothesis. Rejection of the null hypothesis provides evidence that not doing an ALND in women found to have a positive SN results in survival that is not substantially worse than performing an ALND.

An estimate of survival in near optimally treated node-positive women is 70% at 8 years [Fisher 1989]. Another estimate of survival for node-positive women is 76% at 5 years [EBCTCG 1992]. These estimates and exponential survival distribution assumptions are used to compute hazard rates used in subsequent trial size computations. The computed hazard rates for these two survival estimates are 0.0446 and 0.0549, respectively. The former hazard rate estimate is the more conservative and is favored.

Trial size computations are displayed for an accrual rate of 500 eligible patients per year. This accrual rate was estimated from a survey. Alternative follow-up intervals following the completion of accrual of 3 and 5

years also are specified.

The computed accrual times for specified hazard rates, accrual rates, and follow-up times are shown in the following table. The hazard rates for Arm 1 are those computed from survival estimates cited previously. The hazard rate for Arm 2 is 1.3 times the hazard rate for Arm 1. The median and 5 year survivals are computed from the hazard rates and illustrate the differences corresponding to the clinical significance criterion used to design the trial. The trial accrual time is computed from these specifications. The trial size is the trial accrual time multiplied by the accrual rate for eligible patients. The total trial time is the sum of the computed accrual time and the specified follow-up period, and is the earliest the trial can be reported unless terminated early by the DMC.

λ (Hazard rate)		Median Survival		5 Year Survival		Accrual Rate per year	Follow -up	Total Accrual for the Trial		Total Trial Time
1	2	1	2	1	2			Time	Size	
0.0549	0.0714	12.6	9.7	76%	70%	500	3	4.2	2100	7.2
							5	3.3	1650	8.3
0.0446	0.0580	15.5	11.9	80%	75%	500	3	4.7	2350	7.7
							5	3.8	1900	8.8

Using the favored specifications (hazard rate of 0.0446 from the Fisher article and 5 years of follow-up prior to final analysis), the trial size is 1900 patients with a final report at 8.8 years following trial initiation.

There will be five planned formal survival analyses including the final analysis, with an overall type I error probability of 0.05. These formal analyses will take place after each increment of 100 deaths, so that the final analysis is planned for 500 deaths. The first formal analysis is projected to be done 37 months following the start of accrual, and the next three will be done following the cessation of accrual at 54, 70, and 87 months after the start of accrual. The final analysis is projected for 105 months (8.8 years) following the start of accrual. The one-tailed significance levels to be used to judge statistical significance at these formal analyses will be 0.0013, 0.0014, 0.0016, 0.0022, and 0.048, providing an overall one-tailed type I error probability of 0.05. The results of the interim analyses will be used in deciding whether to terminate accrual (if applicable) or publish early in cases where Arm 2 is found to not have significantly worse survival than Arm 1 (the null hypothesis can be rejected). Should Arm 2 exhibit significantly worse survival than Arm 1, then ad hoc tests illustrating the likelihood of Arm 2 eventually having a better outcome will be presented to the DMC as an aid in deciding whether to terminate accrual (if applicable) or publish early based on the futility of Arm 2 ever exhibiting essentially equal or better survival than Arm 1.

A fundamental assumption inherent in the design of this study is that the regional recurrence hazard rate will not be unacceptably high in women with a positive SN who do not undergo ALND. Nevertheless, the specification of what constitutes an unacceptably high regional recurrence hazard rate must take into account the following factors:

(1) It is expected that the regional recurrence hazard for Arm 2 (no ALND) will be higher than for Arm 1 where there has been an ALND.

(2) There will likely be significantly more morbidities associated with the ALND (Arm 1).

(3) There is evidence that a higher hazard rate for regional recurrence is not associated with an increase in the death hazard rate.

(4) The data on which crude estimates of the hazard rate for regional recurrence in women who do not have an ALND is based are not contemporary, were collected incidentally to the assessment of the issue of interest, do not have sufficient follow-up, and do not address the specific conditions of interest in this trial (no ALND when the SN is positive).

These factors, and especially the factors which relate to judgment in the face of a trade-off between choices, mean that an attempt to specify a highly quantitative monitoring plan for the DMC relative to the issue of regional recurrence has a high degree of arbitrariness. Based on input fro m experts the guidance criterion for an excessively high regional recurrence rate is a regional recurrence hazard rate that would result in more than a 20% regional recurrences estimate at five years. The DMC will be provided with analyses of the regional recurrence rates at each meeting. It also will be provided with updates of the literature that has bearing on this issue. The DMC will treat the regional recurrence as a safety issue. It will base its deliberations on the data from this trial, other available data, and the guidance criterion specified.

The primary short-term outcome of interest is a comparison between the arms of the proportion of women having significant morbidity due to axillary surgery. The outcome for each woman will be dichotomous expression of whether a significant ALND-type side effect or complication has occurred. The occurrence of significant ALND-type side effects are defined as occurrence of any of the following side effects: lymphedema, pain in the axillary bed, loss of sensation, decreased range of motion, or infection. Let P_A and P_B be the proportion of women experiencing a significant ALND-type side effect (as defined in the previous sentence) in Arms 1 and 2, respectively. The primary analysis for this short-term outcome will be Fisher's exact test for a difference between P_A and P_B. A worst-case approximate statistical power analysis is based on assuming that P_A is 0.5. Assume a two-sided type I error probability of 0.05, 1900 eligible patients (950 per arm), and a difference of 8%. Under these assumptions, the approximate statistical power is 93%. Exploratory logistic regression analyses of the probability of significant ALND-type side effects (and possibly the components of this composite outcome) using available covariates also will be performed.

The DMC also will assess the adequacy of the accrual rate. The accrual rate estimate will be computed as the median of the monthly accruals in the previous three months. If the monthly accrual rate estimate based on this method following one year of accrual is not consistent with an accrual rate that would yield 500 patients per year, or if the trend in monthly accruals is not consistent with achieving 500 patients per year by the time of 18 months of accrual, then the DMC will be asked to make recommendations regarding an accrual rate problem. These recommendations could address whether to continue the trial, suggestions of trial modifications designed to improve the accrual rate, or other trial modifications consistent with maximizing the likelihood of obtaining an answer to the primary question.

Additional supporting and exploratory statistical models (proportional hazard regression and logistic regression) will be estimated with the primary focus of comparing the arms . The primary additional outcome to be modeled is distant disease-free survival. Additional candidate covariates include: tumor characteristics, tumor size, ICC bone marrow metastasis, histology, and menopausal status.

11 Regulatory and Ethical Considerations

11.1 ACOSOG Membership

The investigator intending to register a patient to this study must be a member in good standing of the American College of Surgeons Clinical Oncology Group (ACOSOG). The procedures for obtaining active status in ACOSOG are described in the membership information found on the ACOSOG web site at http://www.acosog.org.

11.2 NCI Investigator Registration

All enrolling investigators must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (Form FDA 1572 with original signature, current CV, Supplemental Investigator Data Form with original signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch. These forms, along with completion and submission instructions, are available on the ACOSOG web site or by calling the PMB at 301496-5725 Monday through Friday between 8:30AM and 4:30PM Eastern time.

11.3 Clinical Site Eligibility

The clinical site must be formally part of or affiliated with an institution that has active status in ACOSOG or, if this study is open for registration from other cooperative groups, the institution must have active status in the group permitted to register to this study. If the institution has joined ACOSOG then notification of the successful application must have been issued at least 7 days before the first attempt at registration of a patient.

11.4 OHRP Considerations

An ACOSOG member must enroll patients at clinical sites that have a valid assurance number from the United States Office for Human Research Protections (OHRP). Most institutions have a Multiple Project Assurance (MPA), Cooperative Project Assurance (CPA) number or Federalwide Assurance (FWA). If the clinical site does not have such an assurance, the clinical site must apply and obtain an assurance before patients can be enrolled to ACOSOG studies.

Unaffiliated Investigator Agreements (UIAs) are needed from investigators who independently accrue patients on ambulatory protocols outside an institution (e.g., in private practice) but who rely on an institution's IRB for review of ACOSOG protocols.

Information on applying for a FWA may be obtained from the ACOSOG Coordinating Center, by referring to ACOSOG SOP "Applying for OHRP Assurance", or by directly contacting OHRP.

11.5 Institutional Review Board Approval

It is the investigator's responsibility to ensure that this protocol is reviewed and approved by the appropriate IRB. Each clinical site must obtain a letter of approval from the IRB (full board review) prior to screening and registering patients to this study as defined by the following:

- Federal Regulatory Guidelines (Federal Register Vol. 46, 8975, January 27, 1981 as amended in Federal Register Vol. 56, 28029, June 18, 1991 and in Federal Register Vol. 66, 56775, November 13, 2001).
- Office of Protection for Research Risks Report: Protection of Human Subjects (Code of Federal Regulations Title 45, Part 46).

The IRB also must review and approve the site's informed consent document and any other written information provided to the patient prior to its use.

Participating investigators are required to submit a copy of the IRB document indicating approval of the protocol and the consent form as well as a copy of the IRB-approved consent form prior to registering the first patient. For instructions on the submission of these documents, please refer to the IRB Approval SOP (IRB App) found on the ACOSOG web site at http://www.acosog.org/.

If, during the study, it is necessary to amend either the protocol or informed consent document, the investigator will be responsible for ensuring the IRB reviews and approves the amended documents. IRB approval of the amended informed consent document must be obtained before new patients consent to participate in the study using this version of the consent.

11.6 Informed Consent

11.6.1 ACOSOG Preparation of the Model Informed Consent Document

In August 1998, the NCI, the Office for Protection from Research Risks (now OHRP), and the Food and Drug Administration (FDA) formed the NCI Informed Consent Working Group. The group prepared a document with a corresponding template called the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" (see http://cancertrials.nci.nih.gov or http://www.nih.gov/news/pr/oct98/nci-22.htm). The NCI requires that this template must be used in the creation of model informed consent documents for all ACOSOG studies.

11.6.2 Adaptation of the Model Informed Consent Document

For each protocol, the ACOSOG provides a model informed consent document in a file form that can be downloaded for inclusion into a chosen word processing system. The Informed Consent SOP (InfCon SOP) discusses how to adapt the model informed consent document for local use. This model informed consent has been approved for use by the DCT/NCI, and is the only consent document approved for this study. All required elements and NCI required text must be included when adapting the model informed consent to include site-specific text **requirements.** Local IRB adaptations and editorial changes of this document are allowed as long as the meaning or intent of the section is not changed.

When the model informed consent for an ACOSOG protocol is adapted to local requirements, it is the responsibility of that institution to ensure that protocol procedures, especially risks, AEs, and treatment choices, are fully and accurately represented in the local informed consent to be used at the institution.

11.6.3 Informed Consent Process

The investigator or his/her authorized designee will inform the patient or the patient's legally authorized representative of all aspects pertaining to the patient's participation in the study.

The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The informed consent document must be signed and dated by the patient or the patient's legally authorized representative BEFORE the patient can participate in the study. In addition, the investigator will ensure that there is compliance with all institutional requirements for consent form execution. The patient will receive a copy of the consent, and the original will be retained according to local requirements.

11.7 Protection of Patient Rights

11.7.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all patients involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the patient's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the Informed Consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits. The IRB must give full board approval of the protocol and consent documents before the study may begin at a site.

11.7.2 Confidentiality of Patient Data

The clinical site is responsible for the confidentiality of the data associated with patients registered in this study in the same manner it is responsible for the confidentiality of any patient data within its sphere of responsibility. For patients registered to this study, there are additional considerations related to the necessity of sharing of research data with the ACOSOG Coordinating Center and representatives of NCI and OHRP.

The Privacy Rule (Title 45, Code of Federal Regulations, Parts 160 and 164) created as a result of the enactment of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) protects the privacy of individually identifiable health information. The rule's requirements also heighten the protection of patient information by introducing more controls on its use and disclosure. HIPAA refers to patient information as "protected health information" (PHI). PHI includes any information that could identify a person, living or dead. To comply with HIPAA's Privacy Rule, the patient is required to authorize the use and disclosure of his/her PHI by either signing a HIPAA-compliant informed consent document or a separate authorization form created for this purpose. The provisions of the Privacy Rule do not negate the other federal regulations that govern the protection of patient's rights relative to data confidentiality and the use of research data.

11.8 Inclusion of Women and Minorities

The ACOSOG has no data and therefore has no direct evidence regarding the potential for there to be minority-specific effects for the types of patients expected to be enrolled on this study. No literature has been identified that addresses the issue of conclusive minority-specific effects for the issues addressed in this study. A survey of many of the protocols currently accruing cooperative group phase III breast cancer studies was done. The purpose of this survey was to ascertain whether any of these protocols discuss design features based on data showing an expectation of minority-specific effects for any of the issues addressed in these studies, even though these studies tend to address the issues of chemotherapy and hormonal therapy. The background sections of these protocols often report recent analyses addressing minority-specific effects. There were no conclusive data cited or expectations discussed for minority-specific effects.

The ACOSOG has no data and therefore has no basis for projecting the proportions of minority patients to be expected. Therefore, the ACOSOG will base its accrual projection on the projections used in another cooperative group. In the Southwest Oncology Group study S9623, the following proportional allocation of accrual was used. The projected accrual for this study is based on the Southwest Oncology group experience:

Race Category	% Accrual	Projected Accrual
American Indian or Alaska Native	0	0
Asian or Pacific Islander	0	0
Black, not of Hispanic Origin	9	171
Hispanic	5	95
White, not of Hispanic Origin	84	1596
Other or Unknown	2	38
Total	100	1900

The ACOSOG has implemented initiatives to promote the recru itment of minority surgeons and patients into ACOSOG and such initiatives are likely to be in place soon after this study begins accrual and may increase minority participation.

Men are excluded from this study because the number of men with breast cancer is insufficient to provide a statistical basis for assessment of effects in this subpopulation of people with breast cancer.

11.9 Clinical Site Audits

All clinical sites at which patients are enrolled are subject to an on-site audit by ACOSOG in accordance with guidelines provided by and available from the Clinical Trials Monitoring Branch (CTMB) of the NCI. Information on these regulations may be obtained from the CTMB web site at http://ctep.cancer.gov/.

11.10 Clinical Monitoring

This study will be monitored by the current version of the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

12 Surgeon Skill Verification

There are no skill verification procedures for this study.

13 Performance Monitoring

If, based upon the materials submitted, or during participation on this study, an investigator has a possible performance issue, the ACOSOG study committee will review the issues and make recommendations based on its findings to the investigator. It is expected that in most cases, the study committee will work with the investigator to improve performance. However, the study chair and the ACOSOG study committee are empowered to suspend protocol participation, if necessary.

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15 Appendices

15.1 Abbreviations

ACOSOG	American College of Surgeons Oncology Group
AdEERS	Adverse Event Expedited Reporting System AE Adverse Event
ALND	Axillary Lymph Node Dissection
BCT	Breast Conserving Therapy
CDUS	Clinical Data Update System
CFR	Code of Federal Regulatons
cm	Centimeter
CPA	Cooperative Project Assurance
CRF	Case Report Form
CTC	Common Toxicity Criteria
CTEP	Cancer Therapy Evaluation Program
CTMB	Clinical Trials Monitoring Branch
CTV	Clinical Target Volume
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen Receptor
FBAA	Follow-up Breast and Arm Assessment
FDA	Food and Drug Administration
FNA	Fine Needle Aspiration
FWA	Federalwide Assurance
Gy	Gray
H&E	Hematoxylin and Eosin
ICC	Immunocytochemistry
IDB	Investigational Drug Branch
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IVR	Interactive Voice Response
JCRT	Joint Center for Radiation Therapy
LSE	Long Term Surgical Effects
mC	milliCuries
MV	Megavoltage
MPA	Multiple Project Assurance
MRM	Modified Radical Mastectomy
NCCTG	North Central Cancer Treatment Group
NCI	National Cancer Institute
NSABP	National Surgical Adjuvant Breast and Bowel Project Trial
OHRP	Office of Human Research Protection
OIR	Optical Image Recognition
PDF	Portable Document Format
PTV	Planning Target Volume
RM	Radical Mastectomy
RT	Radiotherapy
RW	Registration Worksheet
SAE	Serious Adverse Event
SERMs	Selective Estrogen Receptor Modulators
SN	Sentinel Node
SLND	Sentinel Lymph Node Dissection
SOP	Standard Operating Procedures
SSE	Short Term Surgical Effects
TM	Total Mastectomy
UIAs	Unaffiliated investigator agreements
URL	Universal Resource Locator
WLE	Wide Local Excision

15.2 Staging Reference Selected elements from the AJCC Cancer Staging Manual, 1997 fifth edition:

Stage	Criteria
T0	No evidence of primary tumor.
Tis	Carcinoma in situ: intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no tumor.
T1	Tumor 2 cm or less in greatest dimension.
T1mic	Microinvasion 0.1 cm or less in greatest dimension.
T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension.
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension.
T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension.
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension.
T3	Tumor more than 5 cm in greatest dimension.
T4	Tumor of any size with direct extension to a) chest wall or b) skin.
N0	No regional lymph node metastasis.
N1	Metastasis to movable ipsilateral axillary lymph node(s) (include any N1a, N1bm N1bI, N1bII, N1bIII, or N1bIV).
M0	No distant metastasis.
Stage	**TNM**
I	T1, N0, M0
II	T0, N1, M0; T1, N1, M0; T2, N0, M0; T2, N1, M0; T3, N0, M0

15.3 ECOG/Zubrod Performance Status Scale

ECOG/Zubrod Score	Performance Status
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed < 50% of the day
3	Symptomatic, in bed > 50% of the day but not bedridden
4	Bedridden
5	Dead

15.4 Cancer Trials Support Unit (CTSU) Participation Procedures

15.4.1 Registration / Ramdomization

Before recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit all IRB/regulatory documents to the CTSU Regulatory Office before patient enrollments may proceed. All forms and documents associated with this study can be downloaded from the ACOSOG-Z0011 Web page on the CTSU registered member Web site (http://www.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and all pertinent forms and documents are approved and on file with the CTSU.

Requirements for ACOSOG-Z0011 site registration:

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet
- IRB-approved consent form

Prestudy requirements for patient enrollment on ACOSOG-Z0011:

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed.

CTSU Procedures for Patient Enrollment

Patients registered to this study may undergo either post-operative registration and randomization OR pre-operative registration with intra-operative randomization.

Post-operative Registration and Randomization

Contact the CTSU Patient Registration Office by calling 1-888-462-3009 to alert the CTSU Patient Registrar that an enrollment is forthcoming. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- ACOSOG-Z0011 Registration Worksheet

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 4:30 p.m., Mon-Fri, Eastern time. The registrar will also check the forms for completeness and follow-up with the site to resolve any discrepancies. Once investigator eligibility is confirmed and enrollment documents are reviewed for completeness, the CTSU registrar will enroll the patient via ACOSOG's Web-based registration program. Upon successful registration, an ACOSOG generated confirmation of registration e-mail will be forwarded by CTSU to the enrolling site. The confirmation of registration e-mail will include the patient's treatment assignment and the assigned patient identifier number to be used on all future forms and correspondence.

Pre-operative Registration with Intra-operative Randomization

Pre-registration is necessary in advance of intra-operative randomization. To pre-register the patient, contact the CTSU Patient Registration Office by calling 1-888-462-3009 to alert the CTSU Patient Registrar that an enrollment is forthcoming. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- ACOSOG-Z0011 Registration Worksheet

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 4:30 p.m., Mon-Fri, Eastern time. The registrar will also check the forms for completeness and follow-up with the site to resolve any discrepancies. Once investigator eligibility is confirmed and enrollment documents are reviewed for completeness, the CTSU registrar will enroll the patient via ACOSOG's Web-based registration program. Upon successful registration, an ACOSOG generated confirmation of registration e-mail will be forwarded by CTSU to the enrolling site. The confirmation of registration e-mail will include the assigned patient identifier number to be used on all future forms and correspondence, and an 8-digit 'token' to be used at time of randomization.

Intra-operative randomization is accomplished via ACOSOG's 24-hour automated Interactive Voice Response (IVR) system. CTSU sites should follow the procedures outlined in protocol Section 4.3.2 point #5. Once the token is verified by the system, the randomized treatment arm is given. Complete the ACOSOG-Z0011 Registration Worksheet and fax within 24 hours to the ACOSOG Coordinating Center at 919-668-8466 and the CTSU Data Operations Center at 1888-691-8039.

If a patient is found to be ineligible during surgery (i.e. did not have a positive sentinel node), inform the CTSU Patient Registrar at 1-888-691-8039 and the CTSU will cancel the token.

15.4.2 Data Submission

All case report forms (CRFs) and other documents associated with this study must be downloaded from the ACOSOG-Z0011 Web page located on the CTSU registered member Web site (http://www.ctsu.org). CTSU investigators must use the current version of the protocol-specific ACOSOG-Z0011 forms and adhere to the ACOSOG-Z0011 Schedule of Forms located in the All Forms package link on the CTSU ACOSOG-Z0011 web page.

Effective November 14, 2011, all participating sites will submit patient data via fax to 507-293-3575 for entry by Statistics and Data Center personnel.

15.4.3 Adverse Event (AE) Reporting

This study will utilize the NCI CTC version 2.0 for adverse event assessment. A link to the CTC version 2.0 guidelines is available on the CTSU member Web site. CTSU investigators should employ definitions of adverse events as described in the protocol. All reporting should be conducted within the time frames specified in the protocol. Reports and supporting documentation must be submitted as outlined below.

Submitting Expedited Reports: IMPORTANT: An online AdEERS form cannot be used for surgical intervention only trials, such as ACOSOG-Z0011. Do not attempt to submit a completed form electronically through the AdEERS web site, as the system currently will not permit electronic submission of reports without the completion of Section 4, which requires a pharmaceutical agent. Section 4 Course Information should be left blank. Per Adverse Event Reporting section of the protocol, download the Word version of the Adverse Drug Event Expedited Report (AdEERS) form from the Adverse Events section of the ACOSOG-Z0011 web page located on the CTSU member site. Complete the form and email it directly to ACOSOG at Adeers@surgerytrials.duke.edu. The ACOSOG will fax the form to the NCI upon receipt.

All fatal (Grade 5) AEs (see Section 8.0 of the protocol for details) must be reported by telephone to the ACOSOG Coordinating Center (919) 668-8191 **within 24 hours of the event**. This should be followed by an expedited report within 10 working days.

Your local Investigational Review Board must be informed of all reportable serious adverse reactions.

15.5 Model Informed Consent Document

MODEL CONSENT FORM FOR ACOSOG STUDY Z0011

A randomized trial of axillary node dissection in women with clinical T1 or T2 N0 M0 breast cancer who have a positive sentinel node

WHY AM IBEING ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this study because you have what is known as "early stage" breast cancer that has spread to one of the first few lymph nodes that drain lymphatic fluid from the area around your breast cancer.

It is up to you to decide whether or not to take part in this study. Please read this consent form carefully. Take your time making your decision. We encourage you to talk with your doctor, family, and friends before you decide.

WHO IS CONDUCTING THIS STUDY?

This study is a clinical trial conducted by the American College of Surgeons Oncology Group (ACOSOG). Clinical trials are research studies designed to find better ways to treat diseases like cancer.

(The local institution is responsible for supplying information as to who is conducting the trial locally, suggested content should include the name of contact at the local institution, with phone number and address.)

WHY IS THIS STUDY BEING DONE?

Today, standard medical practice is to look for possible spread of breast cancer to your lymph nodes with an operation called an axillary lymph node dissection (ALND). This operation removes lymph nodes from the middle and lower armpit on the side in which you have cancer. These lymph nodes are called the axillary nodes.

Many research studies have shown that removal of the axillary nodes may not affect how long a patient lives. ALND is important because it lets your doctor know if you have cancer cells in your axillary nodes. Your doctor may use this information to decide on the type of treatment (chemotherapy or hormonal therapy) you receive after your breast cancer surgery. Another possible benefit of ALND is that it may decrease the risk of cancer coming back in your armpit. The number of axillary lymph nodes that must be removed to give your doctor enough information to decide on treatment options is not known. The number of axillary lymph nodes that must be removed to reduce the risk of cancer coming back in your armpit also is not known.

Sentinel lymph node dissection (SLND) is a new procedure that locates and removes the few lymph nodes to which the lymphatic fluid from the tumor site first drains. These lymph nodes are called the sentinel nodes. A patient will usually have from 1 to 4 sentinel nodes. If tumor cells spread, they will usually be found in the sentinel nodes.

Researchers do not know if removing most of your axillary nodes with an ALND is any better than removing just the sentinel nodes. It is possible that SLND is just as good as ALND in the treatment of women with "early stage" breast cancer even when their sentinel nodes contain cancer cells ("positive sentinel nodes"). It is important to find this out because SLND is a less invasive surgical procedure with fewer surgical side effects than ALND. The only way to see which operation is better is to study the procedures in a large group of women who have "early stage" breast cancer.

WHAT IS THE PURPOSE OF THIS STUDY?

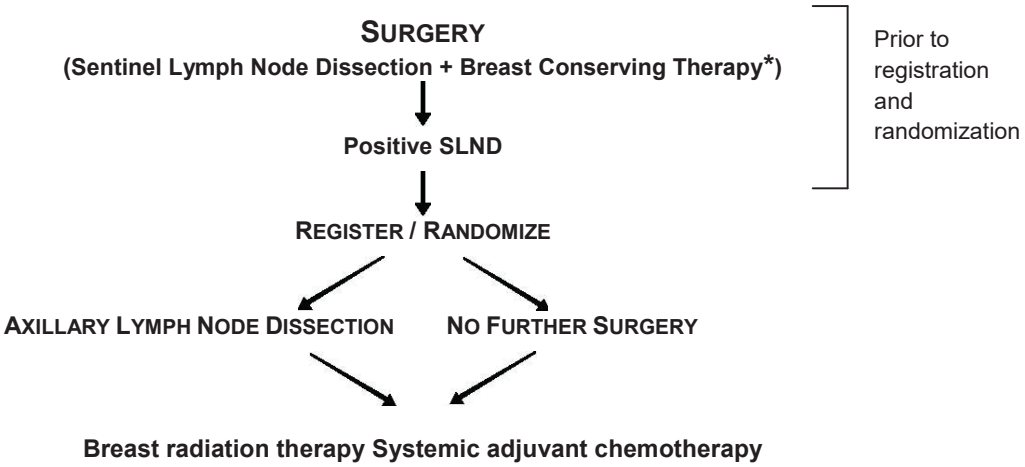
This research study has several goals:

- To see if women who undergo SLND have the same long-term outcome as women who have an ALND even when the sentinel nodes contain cancer cells. We hope that this information will allow surgeons to decide if SLND can safely replace ALND in this situation.
- To compare the surgical side effects of SLND with those of ALND.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 1,900 women from many cancer treatment centers will take part in this study.

WHAT IS INVOLVED IN THE STUDY?



* Women who have undergone breast-conserving therapy are eligible if it was performed less than or equal to 60 days prior to SLND.

Your doctor will explain both the SLND and ALND procedures to you. You should ask your doctor any questions you may have about these procedures.

At the time of your SLND:

- If your sentinel nodes show evidence of cancer on routine examination, you will be eligible for this study which compares SLND to ALND;
- If your sentinel nodes do not show evidence of cancer on routine examination, you will not be eligible for this study; or
- If a sentinel lymph node cannot be found, you will not be eligible for this study

If you decide to join this study*:*
You will be randomly assigned (by a process called randomization) to one of two groups: the SLND Group or the ALND Group. This means that a computer program will put you in the SLND Group or the ALND Group by chance. Neither you nor your doctor will choose which group you are in. You will have an equal chance of being placed in either of the two groups.

> ***If you are in the SLND Group:*** Your sentinel nodes will be located and removed at the time your SLND is performed. No additional axillary lymph nodes will be removed. Your doctor will explain the procedures he or she uses to find sentinel nodes. Your doctor may use a radioactive tracer and/or blue dye procedure to locate your sentinel nodes. Research studies have shown that the radioactive tracer and/or blue dye procedure can accurately identify sentinel nodes in at least 95% of patients. You should ask your doctor any questions you may have about the procedures he or she uses to locate sentinel nodes.
>
> ***If you are in the ALND Group:*** An ALND will be performed after your SLND is complete. Your doctor will remove the lymph nodes that are in the middle and lower areas of your armpit on the side in which you have breast cancer.

Your doctor also will explain the timing of your randomization. Your doctor will use either "post-operative" randomization or "intra-operative" randomization.

In "post-operative" randomization, the pathologist will examine your sentinel nodes for cancer after your sentinel lymph node surgery is over. The pathologist will use a technique called permanent analysis or Hematoxylin and Eosin staining. This test takes several days to obtain results.

If the pathologist finds cancer in your sentinel nodes, you will be randomized to either the SLND Group or the ALND Group. If you are in the SLND Group, no further surgery will be done. If you are in the ALND Group, yo ur doctor will remove the lymph nodes in the middle and lower areas of your armpit in a second operation.

In "intra-operative" randomization**,** the pathologist will examine your sentinel nodes immediately following your sentinel lymph node surgery while you are still in the operating room. The pathologist will use a technique called frozen section analysis or a technique called "touch prep". If the pathologist finds cancer in your sentinel nodes, you will be randomized while still in the operating room. If you are in the SLND Group, no more lymph nodes will be removed. If you are in the ALND Group, your doctor will remove the lymph nodes in the middle and lower areas of your armpit at that time.

The pathologist also will examine your sentinel nodes using permanent analysis when your surgery is over. About 10-15% of patients who do not have cancer in their sentinel nodes detected by frozen section or "touch prep" will have cancer detected by permanent analysis. If you are one of these patients, you will be randomized to either the SLND Group or the ALND Group when these results become available. If you are in the SLND Group, no further surgery will be done. If you are in the ALND Group, your doctor will remove the lymph nodes in the middle and lower areas of your armpit in a second operation.

You should ask your doctor any questions you may have about the timing of randomization he or she uses for the Z0011 study.

WHAT ABOUT MY TREATMENT AFTER SURGERY?

Treatment given after surgery is called adjuvant therapy. Adjuvant therapy for breast cancer can include chemotherapy, hormonal therapy, and/or radiation therapy. After your surgery, you will receive 25-28 treatments of radiation to your involved breast. It will usually be given once a day for five days a week *(except Saturday and Sunday)* for 5 to 5½ weeks. In addition, your doctor may advise you to receive additional adjuvant treatment for your cancer after your surgery.

WHAT TESTS ARE NECESSARY FOR THIS STUDY?

Procedures and tests that are part of regular care are listed in the table below. These procedures and tests will need to be done even if you decide not to join this study.

Procedure/Test (Part of regular care)	Location of Procedure/Test	Timing of Procedure/Test (When done as part of regular care)
Physical examination and history	Out-patient	Usually within 42 days of surgery
Standard blood testing	Out-patient	Usually within 42 days of surgery
Testing for medical clearance for treatment and surgery, including chest x-ray	Out-patient	Usually within 42 days of surgery
Intravenous fluids, which may include antibiotics	In hospital	Before, during, and after surgery as needed
Lumpectomy	Out-patient or In hospital	Same day to 2 day hospital stay (1-2 hour procedure)
Axillary lymph node dissection operation (ALND) may be performed	In hospital	Same day to 2 day hospital stay (1-2 hour procedure)
Radiation Therapy	Out-patient	Each week day for 5 to 5 ½ weeks (30 minute to 1 hour procedure)

The additional procedures and tests that will be performed if you decide to join this study are listed in the table below.

Procedure/Test (Specific to this study)	Location of Procedure/Test	Frequency of Procedure/Test
Symptom assessments, including measurements of shoulder function	Office visit	Before surgery and at scheduled intervals after surgery
Measurement of arm circumference	Office visit	Before surgery and at scheduled intervals after surgery
Radioactive tracer and/or blue dye procedure to locate sentinel nodes	Out-patient or in hospital	Before or during surgery (30 minutes to 1 hour procedure)
Sentinel lymph node dissection (SLND)	In hospital	Same day to 2 day hospital stay (1-3 hour procedure)

HOW LONG WILL IBE IN THE STUDY?

We would like to keep track of your medical condition for the rest of your life to look at the long-term effects of the procedures you will receive in this study. Your doctor may decide to take you off study if:

- Your medical condition changes, or
- New information becomes available affecting your willingness to rema in in the study.

In addition, your participation in the study may end because ACOSOG finds it must limit or stop the study. You also can stop taking part in the study at any time. If you decide to withdraw from the study, you should talk with your doctor first.

WHAT ARE THE RISKS OF BEING IN THE STUDY?

You are at risk for certain side effects while in the study. You should discuss them with your doctor. There may be other side effects that we cannot predict. Your doctor may be able to offer medical treatment to make your side effects less serious and uncomfortable. Many side effects go away shortly after treatment ends, but in some cases side effects can be serious, long lasting, or permanent. Please talk with your doctor about these side effects.

The risks and side effects for the SLND and ALND procedures you may undergo as part of this study are listed below. Likely side effects are those that occur in more than 5% of patients who undergo the procedure. Unlikely side effects are those that occur in 5% or less of patients undergoing these procedures.

For Radioactive Tracer Injection Associated with SLND, risks and side effects include:

Likely

- Exposure to radiation (equal to 1/10th to 1/20th of the annual exposure the average person receives from the sun)
- Tenderness, redness, and pain in the area of the injection site

Unlikely

- Infection at the injection site
- Allergic reaction to the injected solution

For the Blue Dye Injection Associated with SLND, risks and side effects include:

Likely

- Slight blue coloring of the skin around the area of the injection (usually temporary, may be permanent)
- Tenderness and pain in the area of the injection site
- Bluish or greenish discoloration of your urine for several hours after injection

Unlikely

- Infection at the injection site
- Allergic reaction to the injected solution

For the Sentinel Lymph Node Dissection (SLND), risks and side effects include:

Likely

- Time away from work
- Pain
- Mild edema or swelling in your breast and arm that is temporary
- Scarring and/or indentation of your skin in the area of the incision (may be permanent)

Unlikely

- Breast or axillary wound infection (may be serious). If this occurs, it usually happens within 2 weeks after surgery.
- Bleeding or development of a hematoma (a localized blood-filled swelling) in the area of the surgery (rarely serious)

Other Potential Risks of SLND:

- In approximately 5% of SLNDs, the sentinel nodes may not accurately reflect the status of the rest of the lymph nodes in the armpit. It is possible that removing only the sentinel nodes could leave some cancer cells behind. These cells may be destroyed by adjuvant therapy you receive (chemotherapy, hormonal therapy, and/or radiation therapy). It also is possible that these cells will grow in the future and require further surgery and/or therapy.
- Chronic lymphedema is swelling of the arm on the side of the surgery that does not go away. This can be serious. Chronic lymphedema from SLND has not been reported to date.

For the Axillary Lymph Node Dissection (ALND), risks and side effects include:

Likely

- Time away from work
- Pain
- Mild edema or swelling in your breast and arm that is temporary
- Loss of feeling or touch at the incision site and in areas of the upper arm (may be permanent)
- Scarring and/or indentation of your skin in the area of the surgery (may be permanent)
- Bleeding or development of a hematoma (a localized blood-filled swelling) or seroma (mass caused by accumulation of fluid within a tissue or organ) in the armpit on the side of the surgery (rarely serious)

Unlikely

- Chronic lymphedema (may be serious). This is swelling of the arm on the side of the surgery that does not go away.
- Feeling of numbness in the arm that does not go away
- Symptoms from injury to the brachial plexus nerve that involves the entire arm and/or hand on the side of the surgery
- Increased susceptibility to infection in the arm on the side of the surgery if that arm is injured in the future
- Breast or axillary wound infection (may be serious). If this occurs, it usually happens within 2 weeks after surgery.

For the adjuvant Radiation Therapy, risks and side effects include:

Likely

- Fatigue (tiredness) that goes away within a month or two after completion of radiation
- Temporary sunburn-like skin damage within the area of radiation
- Swelling in your breast during treatment and for several months afterwards
- Temporary soreness in the chest wall muscles under the treated breast during and after radiation treatments

Unlikely

- Slight cough and difficulty breathing in the part of the lung under the treated breast (may be long-term)
- Rib fractures
- Pericarditis, *(irritation of the sac surrounding the heart)*, myocarditis *(irritation of the heart muscle),* or rib fractures may occur long after completion of the radiation treatments

Reproductive Risks:

You should not be pregnant or breastfeeding at the time of this surgery. The anesthesia for the surgery and the radioactive tracer and blue dye used to locate the sentinel nodes can affect an unborn baby. You may wish to ask about counseling and more information about preventing pregnancy.

For more information about risks and side effects, ask the researcher or contact _____.
[Reference and attach other material on risks.]

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There may or may not be direct medical benefits to you from your taking part in this study. We hope that information learned from this study will help patients with breast cancer in the future.

A possible benefit of taking part in this study is that you may undergo a SLND, a less invasive surgical procedure with fewer surgical side effects than the standard ALND.

WHAT OTHER OPTIONS DO I HAVE?

Instead of being in this study, you have the following options:

- Lumpectomy alone;
- Lumpectomy and ALND;
- Radiation therapy alone;
- Lumpectomy and radiation therapy;
- Lumpectomy, ALND and radiation therapy;
- Mastectomy with possible post-mastectomy radiation therapy; or
- No treatment

Please talk with your doctor about these and other options before you enter the study. You also should ask your doctor about any options that may become available during this study.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your medical records and study records are confidential but they may be disclosed if required by law.

If the study results are published, no personal information will be identified. This is to ensure that no one will be able to tell that you took part. Records of your progress on the study will be kept in a confidential form at this institution and in a computer file at the American College of Surgeons Oncology Group Coordinating Center (ACOSOG-CC). The confidentiality of the central computer record is carefully guarded. Your research records will include your medical history, results of your exams, reports from your surgery and treatment, and reports of your office visits. Some of the information collected as part of the research also may be included in your medical records.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include:

- The American College of Surgeons Oncology Group (ACOSOG);
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials;
- The local Institutional Review Board (IRB), a group of people who review the research study to protect your rights; and
- Government agencies including the Office of Human Research Protection (OHRP) and the National Cancer Institute (NCI). These agencies may review the research to see that it is being done safely and correctly.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask your doctor about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. *No funds/funds* have been set aside to compensate you in the event of injury. *(The local institution must choose the option that best fits the hospital's situation).* You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

Administration of your treatment will be *(provided free of charge/charged in the usual way).* The parts of the research that involve keeping research records will be paid by those who are organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and

examinations will be *(charged in the usual way/provided at a reduced rate). (The local institution must choose the option that best fits the hospital's situation).*

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You are free to choose to join, to not join, or to leave the study at any time. If you have any questions about the study, you will have a chance to talk with your doctor or one of the study staff about it. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers. Deciding not to participate in this study will not result in any penalty or loss of benefits to which you are entitled.

You may withdraw from the study at any time. Before you withdraw, you should first talk with one of the doctors or nurses involved with the study. Your decision will not affect your medical treatment or your relationships with the medical personnel treating you. If you withdraw from the study, you will still be offered all available care that meets your needs and medical condition.

A Data Monitoring Committee, an independent group of experts, will be reviewing the data from this study on an ongoing basis. Your doctor will tell you about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact *(insert researcher's name and phone number).* For questions about your rights as a research participant or for further information on those rights, contact *(insert name and phone number of Institutional Review Board or patient representative).*

WHERE CAN IGET MORE INFORMATION?

You may call the NCI's Cancer Information Service at:

- 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615

Or visit the NCI's Web site at:

http://www.cancer.gov/

You will get a copy of this form. You also may request a copy of the full study plan.

SIGNATURE

I agree to take part in this research study.

_____ _____

Participant Date

16 Change Summary

Date	Section	Description
01/13/2012	**Z0011 A9**	**ACOSOG Activation**
12/07/2011	**Z0011 A9**	**CTEP Approval**
Begin A9 changes:		
	Title page	**Updated:** Version number and dates **Deleted**: **Update Date: 04/30/2004**
	All pages	**Updated**: Footer; page numbers
	Pg 2 **Contact Information**	**Updated**: Study Chair, Committee Chair, Statistician and Pathology Chair information **Added**: QA Specialist; Protocol Coordinator **Updated**: Contact instructions
	Pg 4 **Cancer Trials Support Unit (CTSU) Address and Contact Information**	**Table has been updated to reflect new data submission instructions.**
	Sec 3, pg 13 **Study Calendar**	**Long-term follow-up has been limited to 10 years from the date of surgery. "until 10 years" has been added to the "Month 36, and then yearly" row in the Follow-up section.**
	Sec 3, pg 13 **Study Calendar**	**"Assessment of long-term surgical side effects including axillary bed and arm effects" has been removed from the "Month 36, and then yearly" row in the Follow-up section. These assessments are no longer required during long-term follow-up.**
	Sec 6.2, pg 21 **Disease-related Assessments**	**Deleted first sentence:** The results of disease-related assessments and treatment directed at breast cancer will be reported at 6, 12, 18, 24, 30, and 36 months following registration, and then yearly until death or lost to follow-up.
	Sec 6.2, pg 21 **Disease-related Assessments**	**Deleted last sentence**: Autopsy reports should be secured and submitted to ACOSOG when possible. A copy of the death certificate also should be submitted. These reports should be submitted using the Miscellaneous Shuttle CRF.
	Sec 6.3, pg 21 **Assessment of Axillary Bed and Arm Effects**	**This section has been revised to reflect changes in the Study Calendar.**
	Sec 7, pg 21 **Evaluation of Outcomes**	**Added to first paragraph:** Patients will be followed for overall survival for a maximum of 10 years from the date of surgery.
	Sec 8.4.2, pg 22 **Long Term Effects**	**This section has been revised to reflect changes in the Study Calendar.**
	Sec 9, pg 25 **Data Considerations**	**This section has been revised to reflect revised CRF availability information and new data submission instructions.**
	Sec 15.4.2, pg 36 **CTSU: Data Submission**	**This section has been revised to reflect new data submission instructions.**
End A9 changes		
	All	Z0011_A8R1 ACOSOG Activation Date
	Title Page	Changed from: Version A8 Activation Date 3/01/2004 Changed to: Version A8R1 Activation Date 4/30/2004 Changed from: Update Date 2/24/2004 Changed to: Update Date 4/30/ 2004

	Page 2	Added: Contact Information for NSABP Investigator, Thomas Julian, MD, and NSABP Coordinator, Joyce Mull. Added: **The Following Groups Have Endorsed This Trial: NCCTG:** Co-chair Barbara Pockaj, MD **NSABP:** Co -chair Thomas Julian, MD **All Cooperative Group members who are not aligned with ACOSOG will enroll patients to this study and submit data via the Cancer Trials Support Unit (CTSU).**
03/01/2004	All	Z0011_A8 ACOSOG Activation Date
02/24/2004	15.4.3	Z0011_A8 update Changed from: Per Adverse Event Reporting section of the protocol, download the Word version of the Adverse Drug Event Expedited Report (AdEERS) form from the Adverse Events section of the ACOSOG-Z0011 web page located on the CTSU member site. Changed to: Per Adverse Event Reporting section of the protocol, download the Word version of the 'ACOSOG Adverse Event Expedited Report Surgical/Intervention Trials form from the Adverse Events section of the ACOSOG-Z0011 web page located on the CTSU member site.
02/11/2004	All	Z0011_A8 CTEP Approval Date
02/03/2004	All	Z0011_A8 CTEP Submission Date
	Title Page	Changed from: Amendment 7 Activation Date Changed to: Version A8 Activation Date Changed from: Amendment 7 CTEP Submission Date Changed to: NCI Version Date
	Page 2	Updated Contact Information table: Breast organ site chair, ACOSOG Statisticians, and Clinical Data Specialist. Added: Copy the ACOSOG Study Coordinator on all correspondence. For patient eligibility or treatment-related questions, send an email to the ACOSOG Study Chair(s). No exemptions or waivers will be granted for patients who do not meet the eligibility criteria. For forms -specific questions, send an email to the ACOSOG Clinical Data Specialist. For specific statistical questions, send an email to the ACOSOG Statisticians. For all other questions, contact the ACOSOG Study Coordinator by phone or email. All calls and correspondence will be triaged to the appropriate representative.
	Page 2-56	Changed footer from: Z0011_A7 Changed footer to: Z0011_A8
	Page 4	Added: Cancer Trials Support Unit (CTSU) Address and Contact Information Table, and CTSU logistical information is found in Appendix 15.4 Participants: American College of Surgeons Oncology Group (ACOSOG) Members North Central Clinical Trials Group (NCCTG) Members NCI Cancer Trials Support Unit (CTSU) investigators. Note that patient enrollments from North American clinical sites that are not aligned with ACOSOG or NCCTG will be conducted via the Cancer Trials Support Unit (CTSU) and all data should be sent to the CTSU. The CTSU will use the *ACOSOG-Z0011* protocol number as required for reporting to ACOSOG and NCI, and when registering patients through the ACOSOG Registrar. CTSU participants and institutions will be instructed to use the *ACOSOG-Z0011* protocol number on all data forms.
	Page 5-6	Updated: Table of Contents
	1.1	Deleted 2nd paragraph: Women who participate in this study (Z0011) also may be registered to study Z0010. However, this is not required for participation in Z0011.
	2	Added: **Each** inclusion and exclusion criterion must be evaluated and **documented** in the patient's medical record. Patient eligibility must be determined by the investigator.
	2.1	Deleted 2nd and 3rd sentences 2nd paragraph: An investigator who is registering patients to this study **before performance of the SLND (intra-operative randomization)** also should register these patients to the ACOSOG Z0010 study, if possible. However, this is not required. Deleted last sentence 3rd paragraph: Patients previously registered to Z0010 will have met eligibility requirements #1 through #8 listed below.
	2.1.7	Changed from: Patient must have ECOG/Zubrod status =2, as documented in patient's medical record. Changed to: Patient must have ECOG/Zubrod status =2, as documented in patient's medical record.
	2.1.11	Changed from: A sentinel lymph node must be identified that contains metastatic breast cancer as documented by frozen section, touch prep, or H&E staining on permanent section. **NOTE:** Patients with metastatic breast cancer identified by immunohistochemistry (IHC) are not eligible. Changed to: A sentinel lymph node must be identified that contains metastatic breast cancer as documented by frozen section, touch prep, or H&E staining on permanent section. (Refer to the Staging Criteria section in the protocol.) **NOTE:** Patients with metastatic breast cancer identified by immunohistochemistry (IHC) are not eligible.
	2.1.14	Changed from: Signed and dated informed consent is obtained **prior to patient registration**. Changed to: Patient or the patient's legally acceptable representative must provide a signed and dated written informed consent prior to registration and any study-related procedures.
	2.1.15	Added: Patient must provide written authorization to allow the use and disclosure of their protected health information. **NOTE:** This may be obtained in either the study-specific informed consent or

		in a separate authorization form and must be obtained from the patient prior to study registration.
	2.3 (old version)	Deleted section: The patient must have the ability to understand and the willingness to sign a written informed consent document. **Prior to registration**, each patient must provide signed informed consent. The **original** signed informed consent should be placed in the patient's study records or medical chart. A **copy** of the signed informed consent document must be given to the patient.
	2.3	Added section: For this study, patients will be staged according to the AJCC Cancer Staging Manual, 5th edition, 1997 (See Appendix for *Staging Reference).* NOTE: In the 5th edition, specific criteria for micrometastatic lymph node deposits are not defined. Although the 6th edition of the AJCC Cancer staging manual defines micrometastases as tumor deposits greater than 0.2mm but not greater than 2.0mm in largest dimension, this definition is not used to determine eligibility for Z0011. Therefore, for this study, a SLN with a micrometastatic tumor deposit < 0.2mm will also be considered a positive SLN.
	4.1	Changed from: This section applies to clinical sites that have both ACOSOG study Z0010 and study Z0011 open. Changed to: This section applies to clinical sites that have both ACOSOG Study Z0010 and Study Z0011 open. Deleted last sentence 1st paragraph: Clinical sites are requested to register patients participating in Z0011 to Z0010 as well, whenever possible. Deleted 2nd paragraph: Patients who are to be registered to both Z0010 and Z0011 must sign a separate informed consent for each study. For patients to be randomized intra-operatively to Z0011, the patient must sign the informed consent for Z0011 prior to the surgeon performing the SLND for Z0010. To randomize a patient post-operatively to Z0011, sites should assess a patient's eligibility to Z0011 after completion of SLND for Z0010 and obtain informed consent for Z0011. Then, sites should register the patient to Z0011 and obtain randomized arm. Added 2nd paragraph: The accrual goal for ACOSOG Study Z0010 was met and the study was permanently closed to accrual on 5/30/2003. All patients currently on the study must continue to be followed according to protocol specifications. Annual IRB review and approval of the protocol and consent form must continue until all registered patients have completed the follow-up phase of the study.
	5.3.2	Changed from: A patient with tumors located in the medial hemisphere of the breast that show a complete absence of drainage to the axilla by lymphoscintigram or by absence of elevated gamma counts will be discontinued from the study and will not be followed. Changed to: A patient with tumors located in the medial hemisphere of the breast that show a complete absence of drainage to the axilla by lymphoscintigram or by absence of elevated axillary lymph node gamma counts will be discontinued from the study and will not be followed.
	8	Deleted: Refer to the ACOSOG Adverse Event Reporting Guidelines at http://www.acosog.org for additional information.
	8.4.1	Changed 2nd sentence 1st paragraph from: The SSE-CRF will be used to report the status of the patient's AEs during the 30-day period following the last study related operation. Changed 2nd sentence 1st paragraph to: The SSE-CRF will be used to report the status of the patient's AEs during the 30-day period following the last study-related operation. Changed 5th bullet 2nd paragraph from: Neuropathy-sensory (axillary paresthesia and/or interocostobrachial nerve paresthesia) Changed 5th bullet 2nd paragraph to: Neuropathy-sensory (axillary paresthesia and/or intercostobrachial nerve paresthesia)
	8.4.2	Changed 2nd sentence 1st paragraph from: The LSE-CRF will be used to report the status of the patient's AEs assessed at months 6, 12, 18, 24, 30 and 36, and then yearly, following the last study related operation. Changed 2nd sentence 1st paragraph to: The LSE-CRF will be used to report the status of the patient's AEs assessed at months 6, 12, 18, 24, 30 and 36, and then yearly, following the last study-related operation.
	8.5.1	Changed 1st sentence from: All unexpected AEs related to surgical interventions will be reported using the AE-CRF. Changed 1st sentence to: All unexpected AEs **related to surgical interventions** will be reported using the AE-CRF.
	8.6	Changed from: An expedited adverse event report requires submission to NCICTEP via the AdEERS web application or the Adverse Event Expedited Report – Single Agent paper template. Reports should be submitted within the timeframes specified below. Assistance for using AdEERS or for completion of the AdEERS templates is available at http://ctep.cancer.gov/. Failure to report SAEs in a timely manner may result in suspension of the investigator's permission to perform clinical research under Investigational New Drug applications (INDs) sponsored by the NCI Division of Cancer Treatment and Diagnosis. SAE reporting is in addition to and does not supplant the reporting of AEs as part of the data submission requirements for the study. Changed to: An expedited adverse event report requires submission to ACOSOG. The new Word version of the AdEERS form is available on the ACOSOG web site at www.acosog.org. This Word document can be downloaded, completed, and emailed to ACOSOG at AdEERS@surgerytrials.duke.edu . The ACOSOG will fax the form to the NCI upon receipt. Failure to report AEs in a timely manner

		may result in suspension of the investigator. AE reporting is in addition to and does not supplant the reporting of adverse events as part of the data submission requirements for the study.
	8.6.1	Deleted table subtitle: **Phase 2 or Phase 3 Studies**
	8.6.3	Changed from: Access the CTEP home page at http://ctep.cancer.gov/. Click on "Reporting Guidelines". Then, click on "Adverse Event Expedited Reporting System (AdEERS)". Under AdEERS templates, click on "Single Agent Template". Print out and complete the paper template and submit completed report. **NOTE: For surgical only studies, Section 4 -Course Information will remain blank. DO NOT attempt to submit a completed form electronically through the AdEERS web site, as the system currently will not permit electronic submission of reports without the completion of Section 4.** Changed to: Expedited adverse event reporting in NCI trials utilizes the AdEERS, "The Adverse Event Expedited Reporting System" An online AdEERS form cannot be used for surgical intervention only trials, such as Z0011 **DO NOT attempt to submit a completed form electronically through the AdEERS web site, as the system currently will not permit electronic submission of reports without the completion of Section 4, which requires a pharmaceutical agent.** Go to the ACOSOG web site at www.acosog.org. Click on the link for "Protocols and Adverse Event Links." Click on the link for "AdEERS for all other protocols." Save the Word form to a local computer and complete according to the instructions provided. E-mail the completed form as an attachment to AdEERS@surgerytrials.duke.edu . **The site is no longer required to fax a copy of the AdEERS form to the National Cancer Institute. The ACOSOG will fax the form to the NCI upon receipt.**
	8.6.4	Deleted 1st table row (old version): **NCI:** Completed expedited reports should be sent to Investigational Drug Branch (IDB), PO Box 30012, Bethesda, MD, 20824 or by fax to 301 230-0159. To make a telephone report, contact NCI at 301 230-2330, available 24 hours a day (recorder after hours from 5:00 PM to 9:00 AM EST). Changed 1st table row (this version) from: **ACOSOG:** A copy of all expedited AE reports should be sent to the ACOSOG Coordinating Center by fax at 919 668-7122. All fatal (Grade 5) AEs should be reported by telephone within 24 hours of the event. To make a telephone report, contact ACOSOG at 919 6688400, available 24 hours a day (recorder after hours from 5:00 PM to 9:00 AM EST). Changed 2nd table row (this version) to: **ACOSOG:** Microsoft Word form of AdEERS should be completed and submitted via email at AdEERS@surgerytrials.duke.edu . For paper submission: A copy of expedited adverse event reports can be sent to the ACOSOG Coordinating Center by fax at (919) 668-7156. All fatal (Grade 5) adverse events should be reported by telephone within 24 hours of the event. To make a telephone report, contact ACOSOG at (919) 668-8191, available 24 hours a day (recorder after hours from 5:00 PM to 9:00 AM EST).
	9	Deleted 2nd sentence: This can be found by following the link labeled "Protocols".
	9.1.1 (old version)	Deleted subsection number: 9.1.1 Changed section title from: Data Form Completion and Submission Guidelines Changed section title to: Case Report Form Completion and Submission Guidelines Added last 2 sentences:**NOTE**: The CRF cannot be used in lieu of the patient's medical record. The CRF is used for transcription of source documentation FROM the preexisting medical record **only**.
	11.2-11.9 (old version)	Changed from: 11.2-11.9 Changed to: 11.2-11.10
	11.2 (this version)	Added: All enrolling investigators must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (Form FDA 1572 with original signature, current CV, Supplemental Investigator Data Form with original signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch. These forms, along with completion and submission instructions, are available on the ACOSOG web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30AM and 4:30PM Eastern time.
	11.4	Changed 1st sentence from: An ACOSOG member must enroll patients at clinical sites that have a valid assurance number from the United States Office for Human Research Protection (OHRP). Changed 1st sentence to: An ACOSOG member must enroll patients at clinical sites that have a valid assurance number from the United States Office for Human Research Protections (OHRP). Deleted last sentence 2nd paragraph: UIAs are only applicable when the study interventions can be performed within the setting of a physician's office. Changed 3rd paragraph from: Information on applying for a FWA may be obtained from the ACOSOG Coordinating Center or by referring to ACOSOG SOP "Applying for OHRP Assurance". Changed 3rd paragraph to: Information on applying for a FWA may be obtained from the ACOSOG Coordinating Center, by referring to ACOSOG SOP "Applying for OHRP Assurance", or by directly contacting OHRP.
	11.5	Changed 2nd sentence 1st paragraph from: Each clinical site must obtain a letter of approval from the IRB (full board review) prior to registering patients to this study as defined by the following Changed 2nd sentence 1st paragraph to: Each clinical site must obtain a letter of approval from the

		IRB (full board review) prior to screening and registering patients to this study as defined by the following Changed 2nd paragraph from: The IRB also must review and approve the site's informed consent document and any other written information provided to the patient prior to any registration of patients. Changed 2nd paragraph to: The IRB also must review and approve the site's informed consent document and any other written information provided to the patient prior to its use. Changed 3rd paragraph from: A copy of the IRB approval letter for the protocol and informed consent document must be provided to ACOSOG prior to registering the first patient. Changed 3rd paragraph to: Participating investigators are required to submit a copy of the IRB document indicating approval of the protocol and the consent form as well as a copy of the IRB-approved consent form prior to registering the first patient. For instructions on the submission of these documents please refer to the IRB Approval SOP (IRB App) found on the ACOSOG web site at http://www.acosog.org/.
	11.6.3	Changed 2nd paragraph from: The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The informed consent document must be signed and dated by both the investigator or his/her designee and the patient or the patient's legally authorized representative BEFORE the patient can participate in the study. The patient will receive a copy of the signed and dated document, and the original will be retained in the patient's study file or medical record. Changed 2nd paragraph to: The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The informed consent document must be signed and dated by the patient or the patient's legally authorized representative BEFORE the patient can participate in the study. In addition, the investigator will ensure that there is compliance with all institutional requirements for consent form execution. The patient will receive a copy of the consent and the original will be retained according to local requirements.
	11.7.2	Deleted last sentence 1st paragraph: The patient grants permission to share research data with these entities in the consent document. Federal regulations govern the protection of patient's rights relative to data confidentiality and use of research data. Added 2nd paragraph: The Privacy Rule (Title 45, Code of Federal Regulations, Parts 160 and 164) created as a result of the enactment of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) protects the privacy of individually identifiable health information. The rule's requirements also heighten the protection of patient information by introducing more controls on its use and disclosure. HIPAA refers to patient information as "protected health information" (PHI). PHI includes any information that could identify a person, living or dead. To comply with HIPAA's Privacy Rule, the patient is required to authorize the use and disclosure of his/her PHI by either signing a HIPAA compliant informed consent document or a separate authorization form created for this purpose. The provisions of the Privacy Rule do not negate the other federal regulations that govern the protection of patient's rights relative to data confidentiality and the use of research data.
	15.4	Added section: Cancer Trials Support Unit logistics
	15.5 (15.4 old version)	Changed title from: Sample Consent Form for ACOSOG Study Z0011 Changed title to: Model Consent Form for ACOSOG Study Z0011 Added in 2nd bullet 3rd paragraph: The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials
	16	Changed section heading from: Revision History Changed section heading to: Change Summary
11/01/2002	All	Z0011_A7 Activation Date
10/24/2002	All	Z0011_A7 CTEP Approval Date
10/16/2002	All	Z0011_A7 CTEP Submission Date
09/26/2001	All	Amendment #6, Revision 1 (A6R1)
09/26/2001	All	Amendment #6, Revision 0 (A6R0)
07/11/2001	All	Amendment #5, Revision #1 (A5R1)
03/07/2001	All	Amendment #5, Revision 0 (A5R0)
12/11/2000	All	CTEP approval of Amendment #5 (A5R0)
07/03/2000	Part 3	Amendment #4: Administrative
03/29/2000	All	Amendment #3: Activation Amendment, Administrative
03/03/2000		Amendment #2: Administrative
04/30/1999		Amendment #1: Activation Amendment, Administrative