Therapeutic Area Data Standards User Guide for Breast Cancer

Version 1.0 (Provisional)

Prepared by the

CFAST BrCa Team

Notes to Readers

- This is the provisional version 1.0 of the Therapeutic Area Data Standards User Guide for Breast Cancer.
- This document is based on CDASH Standard v1.1, SDTM v1.4 and SDTMIG v3.2, and ADaM v2.1 and ADaMIG v1.0.
- The TAUG-BrCa v1.0 package includes this user guide and a set of CDASH metadata

Revision History

Date	Version	Summary of Changes
2016-05-16	1.0 Provisional	Changes made from public review comments *A list of comments and the CDSIC disposition is available on the CDISC website*
2015-11-02	1.0 Draft	Draft for Public Review

See Appendix G for Representations and Warranties, Limitations of Liability, and Disclaimers.

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1 Introduction

This Therapeutic Area Data Standards User Guide for Breast Cancer (TAUG-BrCa) was developed under the Coalition for Accelerating Standards and Therapies (CFAST) initiative.

CFAST, a joint initiative of the Clinical Data Interchange Standards Consortium (CDISC) and the Critical Path Institute (C-Path), was launched to accelerate clinical research and medical product development by facilitating the establishment and maintenance of data standards, tools, and methods for conducting research in therapeutic areas important to public health. CFAST partners include TransCelerate BioPharma Inc. (TCB), the U.S. Food and Drug Administration (FDA), and the National Cancer Institute Enterprise Vocabulary Services (NCI EVS), with participation and input from many other organizations. See http://www.cdisc.org/cfast-0 for a list of CFAST participating organizations.

CDISC has developed industry-wide data standards enabling the harmonization of clinical data and streamlining research processes from protocol (study plan) through analysis and reporting, including the use of electronic health records to facilitate study recruitment, study conduct, and the collection of high quality research data. CDISC standards, implementations, and innovations can improve the time/cost/quality ratio of medical research, to speed the development of safer and more effective medical products and enable a learning healthcare system.

The goal of the CFAST initiative is to identify a core set of clinical therapeutic area biomedical concepts and endpoints for targeted therapeutic areas and translate them into CDISC standards to improve semantic understanding, support data sharing, and facilitate global regulatory submission.

1.1 Purpose

The purpose of this TAUG-BrCa is to describe how to use CDISC standards to represent data pertaining to breast cancer studies. The focus of this version 1.0 (v1.0) of the TAUG-BrCa is on clinical trials of drugs to treat invasive breast cancer in neoadjuvant, adjuvant, and metastatic settings. See Appendix A for the project proposal that was approved by the CFAST Steering Committee.

The TAUG-BrCa v1.0 provides advice and examples for Clinical Data Acquisition Standards Harmonization (CDASH), submission data based on the Study Data Tabulation Model (SDTM), and the Analysis Data Model (ADaM), including:

- Sample case report forms (CRFs) compliant with CDASH, annotated with CDASH and SDTM variables
- CDASH metadata for the sample CRFs (included in the CDASH Metadata folder of the posting package)
- Guidance on which domain models and datasets from the SDTM Implementation Guide for Human Clinical Trials (SDTMIG) to use in representing collected data
- Examples of SDTM datasets, with text describing the situational context and pointing out records of note
- Cross-implementation variable definition metadata for non-standard (Supplemental Qualifier) variables used in example SDTM datasets and/or CRF mapping annotations
- Analysis datasets compliant with ADaM, with dataset- and variable-level metadata
- Table shells illustrating some kinds of statistical analysis that can be represented in the ADaM datasets

CDISC standards are freely available at www.cdisc.org. It is recommended that implementers consult the foundational standards prior to implementing these breast cancer clinical data standards.

This TAUG-BrCa v1.0 describes common kinds of data needed for breast cancer studies, so that those handling the data (e.g., data managers, statisticians, programmers) understand the data and can apply standards appropriately. These descriptions include the clinical situations from which the data arise, and the reasons these data are relevant for breast cancer.

The TAUG-BrCa v1.0 strives to define biomedical concepts unambiguously, so that consistent terminology can be used in breast cancer studies to enable aggregation and comparison of data across studies and drug programs, and so that metadata for these biomedical concepts can likewise be defined.

A biomedical concept is a unit of knowledge created by a unique combination of the characteristics that define observations of real world clinical research phenomena. A biomedical concept represents healthcare and/or clinical research knowledge that borrows from medical knowledge, statistical knowledge, Biomedical Research Integrated Domain Group (BRIDG). Metadata for biomedical concepts include the properties of the data items that are parts of the biomedical concepts, controlled terminology for those data items, and the ways in which the biomedical concepts relate to each other.

Biomedical concepts covered in this guide were selected from concepts identified by one or more stakeholders as important, which were not addressed or not completely addressed by existing CDISC implementation guides. This user guide does not provide guidance on what data is needed for regulatory submission or approval; it only provides advice on how to represent data in a standard form.

To reiterate: It is important to note that the choice of biomedical concepts included in this user guide is not intended to influence sponsor decisions as to what data to collect. The examples included are intended to show how particular kinds of data can be represented using CDISC standards. This user guide emphasizes that ***examples are only examples and should not be over-interpreted***. For guidance on the selection of biomedical concepts and endpoints, please refer to the appropriate clinical and regulatory authorities.

Clinical guidelines, articles, and other works consulted by the team during the creation of this document are referenced where appropriate, using the American Medical Association (AMA) style for citation. For a full list of references, see Appendix F.

1.2 Organization of this Document

The organization of this document differs slightly from other TAUGs in that the management of the disease is included in the same section as disease assessments, as opposed to being touched upon briefly as part of routinely collected data. This document is therefore divided into the following sections:

- Section 1, Introduction, provides an overall introduction to the purpose and goals of the Breast Cancer project.
- Section 2, Overview of Breast Cancer, provides an overview of the Breast Cancer Therapeutic Area in terms of Intent, Settings, and Endpoints
- Section 3, Subject and Disease Characteristics, covers data that are usually collected once at the beginning of a study.
- Section 4, Disease Management and Assessments, covers data related to the ongoing treatment of breast cancer, and data that are used to evaluate disease severity, control, or progression. These are usually collected repeatedly during a study, and may be used as or for the derivation of efficacy and/or safety endpoints.
- Section 5, Analysis Data, includes key data analysis biomedical concepts for a breast cancer study.
- Appendices provide additional background material and describe other supplemental material relevant to breast cancer.

1.3 Concept Maps

This document uses concept maps to explain clinical processes and biomedical concepts. Concept maps, also sometimes called mind maps, are diagrams that include “bubbles” representing concepts/ideas/things and labeled arrows that represent the relationships between the concepts/ideas/things. They are generally easier to draw and more accessible than more formal modeling diagrams, such as Unified Modeling Language (UML) diagrams.

The diagrams in this document use the following coding for classification of concepts:

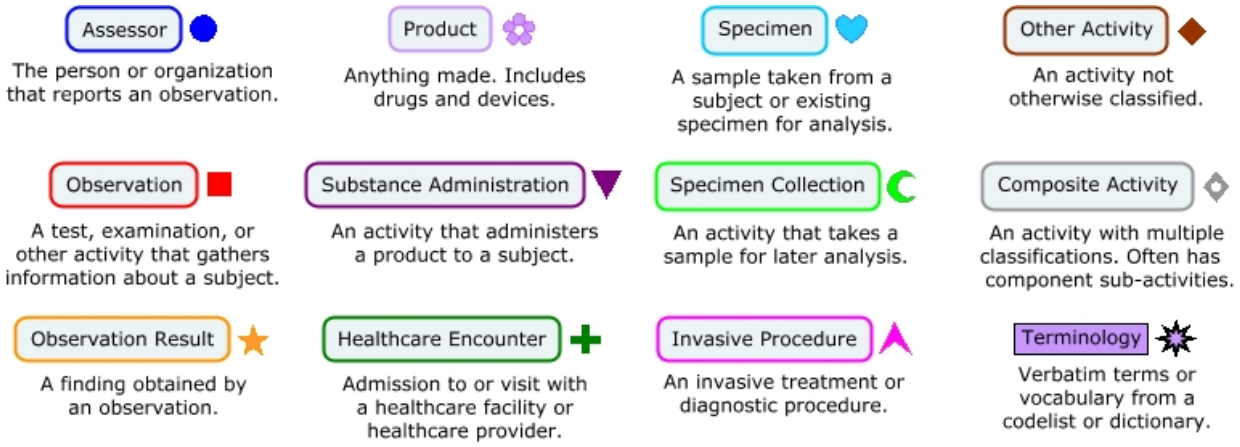


Figure 1: Concept Classification Key for Concept Maps

This classification is based on classes in the BRIDG model (available at http://bridgmodel.nci.nih.gov/). These color-symbol pairs have been used to highlight kinds of things that occur commonly in clinical data and therefore give rise to common patterns of data. Some concepts are not coded; they have a thinner, black outline, and no accompanying symbol. These may include the subject of an observation, as well as characteristics, or attributes, of the coded concepts.

1.4 Controlled Terminology

CDISC Controlled Terminology is a set of standard value lists that are used throughout the clinical research process, from data collection through analysis and submission. Controlled terminology is updated quarterly by the CDISC Terminology Team and published by the National Cancer Institute's Enterprise Vocabulary Services (NCI EVS) at: http://www.cancer.gov/cancertopics/cancerlibrary/terminologyresources/cdisc.

Although the examples in CDISC data standards try to appear plausible, including using controlled terminology where available, they should not be regarded as a definitive source for actual data or for controlled terminology. Some codelists and/or values applicable to biomedical concepts and data elements in this document may still be in development at the time of publication. Some examples may use values that appear to be controlled terminology, but that are actually generic or "best guess" placeholders. Readers should consult the current CDISC Controlled Terminology (available at the link above) as the ultimate authority for correct controlled terminology codelists and values.

1.5 Relationships to Other Standards

This section describes the relationship of this document to other standards, whether CDISC or external.

This document does not replace the foundational CDISC standards or their implementation guides. Users should read those standards and implementation guides before applying the advice in this user guide.

CDISC data standards are living documents. Due to differing update cycles, some of the modeling approaches and controlled terminology presented in the examples in this document may become outdated before the next version is released.

Some kinds of data (e.g., demography, subject characteristics, substance use, reproductive history, adverse events) are already sufficiently covered by the existing standards and can be used in breast cancer studies without additional development or customization. These kinds of data are not discussed in this document.

The SDTM Examples for Oncology Use Cases is heavily referenced by certain sections within this document. It is available at: http://wiki.cdisc.org/x/5yuyAQ.

1.6 Known Issues

- A number of CRFs were proposed for this document, but have been deferred to a later version due to unresolved modeling issues. These include staging, pathology/histology, prior antineoplastic therapy, and infusion drugs (both as concomitant/prior medication and as study treatment).
- In this document, the abbreviation "PR" sometimes stands for the "Procedures" domain, sometimes for "progesterone receptor," and sometimes for "partial response." The reader is cautioned to consider the context when interpreting these abbreviations.
- **Non-Standard Variables:** This document has adopted the practices outlined in the proposed SDTMIG Section 8.4.4, Alternative Representation of Non-Standard Variables (also called the NSV Proposal; it was circulated for public review as part of SDTMIG v3.3 Batch 2). Accordingly, SDTM-based examples containing sample data requiring the use of a variable outside the standard set of variables included in the SDTM v1.4 are represented not with Supplemental Qualifier records, but with non-standard variables (NSVs) appended to the end of the parent domain, followed by sample value-level metadata for the NSVs. In order to avoid confusion between standard variables and NSVs, NSVs have been rendered visually distinct, as shown below, with white text on black in the header row, and separated from the standard variables by a small space.

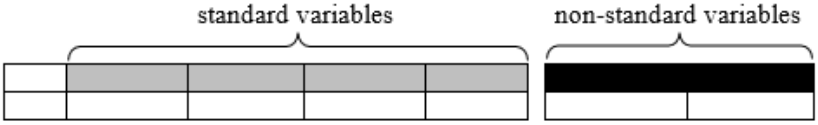


Figure 2: Visual Presentation of Non-Standard Variables in This Document

A list of all NSVs used in this document, and the variable-level metadata that might become normative for the NSVs should they be promoted to standard variables, is given in Appendix D.

- **Treatment Regimens:** The strategy used to treat breast cancer is often a "regimen" that may consist of multiple drugs or of drug treatment combined with radiation and/or surgery.
    - The SDTMIG does not give clear guidance on how to indicate that multiple treatments comprise a regimen. In this document, the relationship among drug treatments given together and considered to be part of a regimen has been represented by assigning a common value of the variable --GRPID (e.g., CMGRPID) to components of the treatment regimen. This solution does not address grouping drug treatments with radiation or surgical treatments, since the latter would be represented in a different domain (PR) than the drug treatments. A currently available solution is to use the Related Records (RELREC) dataset to group all the component treatments. A new solution to indicate that interventions are part of a regimen is under discussion.
    - Breast cancer studies may collect regimen-level data, such as best response to the regimen. An SDTM structure for linking such data to a regimen, rather than to individual treatments in the regimen, has not yet been devised.
- **Radiation Location Category:** Radiation therapy interventions can be characterized based on the subject's disease process and corresponding treatment strategy (i.e., targeted radiation vs. whole body). While "Anatomical Location" provides precise location(s), "Radiation Location Category" describes the clinical classification of the location as it relates to the subject's disease. "Local" is defined as radiation treatment restricted to the site of cancer origin. "Regional" is defined as radiation targeting disease that has extended beyond the local site, spreading to adjacent tissues and/or regional lymph nodes. "Distant" is defined as radiation targeting cancer cells that have spread from the site of the primary tumor to distant organs/lymph nodes. This issue was addressed in the TAUG by using the non-standard variable PRRRLTLC to capture this information in addition to the anatomical location (PRLOC) variable.
- **Line of Therapy**: Due to the complexity of defining a standard definition and representation in SDTM, line of therapy for prior/on-study medications will not be addressed in this version of the TAUG. However, this topic will be revisited for discussion and considered for future versions.
- **Method of Scoring**: In Section 3.3.1 Example 1, controlled terminology has been developed for scoring systems such as Allred, H-score, and Remmele score. SDTM examples showing these scoring systems is planned for a future version of this user guide
- **Best Overall Response**: There are planned discussions on the modeling of this variable. The user is cautioned that this, therefore, may be subject to change.

- **If Tumor Is Inevaluable, Reason Not Done (Target and Non-Target Lesions):** Current modelling of tumor state of inevaluable shows that the result will be missing, status will be NOT DONE, and the reason is mapped to the --REASND variable. This modelling does not capture that the tumor was inevaluable. At the time of publication there were ongoing discussions on how best to model this data. The user is cautioned that the current modelling may therefore be subject to change.
- **Use of the PARQUAL Variable:** Some ADaM examples make use of PARQUAL, a proposed variable with restricted defined usage currently under consideration by the CDISC ADaM team. Note, however, that this variable is incompatible with the current ADaMIG, which states, "PARAM must include all descriptive and qualifying information relevant to the analysis purpose of the parameter."

2 Overview of Breast Cancer

Breast cancer is a solid tumor cancer arising in the epithelial cells of the breast, most commonly the milk ducts or glands. Breast cancer is the most frequently diagnosed cancer in women worldwide, in both developed and developing countries. It is the leading cause of cancer death in women, accounting for 23% of total cancer cases and 14% of cancer deaths.[1] In the U.S., breast cancer accounts for 29% of newly diagnosed cancers and 15% of cancer deaths in women.[2] Breast cancer also occurs in men, but it is rare.

The figure below describes breast cancer treatment in terms of the intent and setting and endpoints associated with these settings. More detailed information can also be found in Appendix E.

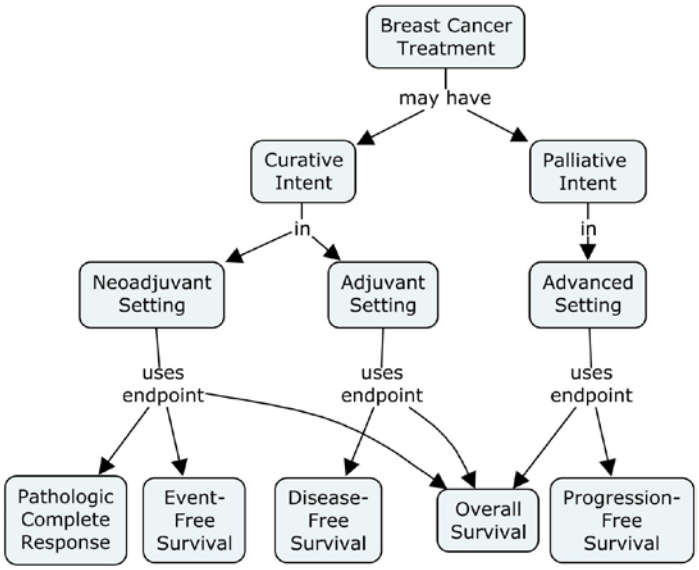


Figure 3: Treatment Settings in Breast Cancer

This document is organized by kinds of data collected in clinical trials, and most kinds of data would be collected in trials in all treatment settings, though with different purposes. For example, pathology data on excised tumors is part of disease history for studies in the adjuvant or advanced settings; in the neo-adjuvant setting, however, this data can be used in determining the endpoint complete pathologic response.

Some of the examples in this document represent data for particular settings, while others would apply to multiple settings:

Use Case	Example	Neoadjuvant	Adjuvant	Advanced
Estrogen receptor status	Section 3.3.1 Example 1	X	X	X
Gross pathology	Section 3.3.1 Example 2	X	X	
Prior anti-neoplastic therapy	Section 3.4.1 Example 1			X
Prior radiotherapy	Section 3.4.1 Example 2			X

Use Case	Example	Neoadjuvant	Adjuvant	Advanced
On-study surgeries	Section 4.1.1 Example 1	X		X
On-study radiotherapy	Section 4.1.1 Example 1	X	X	X
Tumor identification: target lesions	Annotated CRFs in Section 4.2.1*	X		X
Tumor identification: non-target lesions		X		X
Tumor identification: new lesions		X	X	X
Disease response		X		X
Tumor imaging and assessment	Section 4.2.1 Example 1			X
	Section 4.2.1 Example 2			X
Disease response	Section 4.3.1 Example 2			X
	Section 4.3.1 Example 2	X		

** Note: Section 4.2.1 deals primarily with data collection in an advanced setting. CRFs in a neoadjuvant or adjuvant setting could be somewhat simpler.*

Endpoint	Setting	TAUG Reference
Pathologic Complete Response (pCR)	Neoadjuvant	Not included*
Event-Free Survival (EFS)	Neoadjuvant	Analysis Section 5.1.1.3
Disease-Free Survival (DFS)	Adjuvant	Analysis Section 5.1.1.4
Overall Survival (OS)	Neoadjuvant, Adjuvant, Advanced	Analysis Section 5.1.1.2
Best Overall Response	Advanced	Analysis Section 5.1.2.1
Duration of Response	Advanced	Analysis Section 5.1.1.5
Progression-Free Survival (PFS)	Advanced	Analysis Section 5.1.1.1

** Pathologic Complete Response (pCR) is not described in the analysis section because the final analysis of a binary endpoint is simple, and the derivation of the endpoint depends on the definition used, which will vary by study.*

3 Subject and Disease Characteristics

Risk factors for breast cancer include sex, age, family history, early menarche, late menopause, postmenopausal obesity, use of combined estrogen and progestin menopausal hormones, cigarette smoking, and alcohol consumption.[3] The etiology of breast cancer is influenced by diet as well as hormonal and reproductive factors.[4] Individual sponsors/protocols may collect other relevant information (e.g., more granular ethnicity) as needed. Many of the risk factors for breast cancer can be traced back to the cumulative exposure of the breast to estrogen and progesterone, which influence the rate of cell division. Cell proliferation of breast epithelial cells and a series of genetic changes such as activation of oncogenes and inactivation of tumor suppression genes ultimately lead to development of a malignant phenotype. A small proportion of cases of breast cancer (5-10%) are directly related to inherited (germline) mutations in the *BRCA1* and *BRCA2* genes.[5]

3.1 Diagnosis

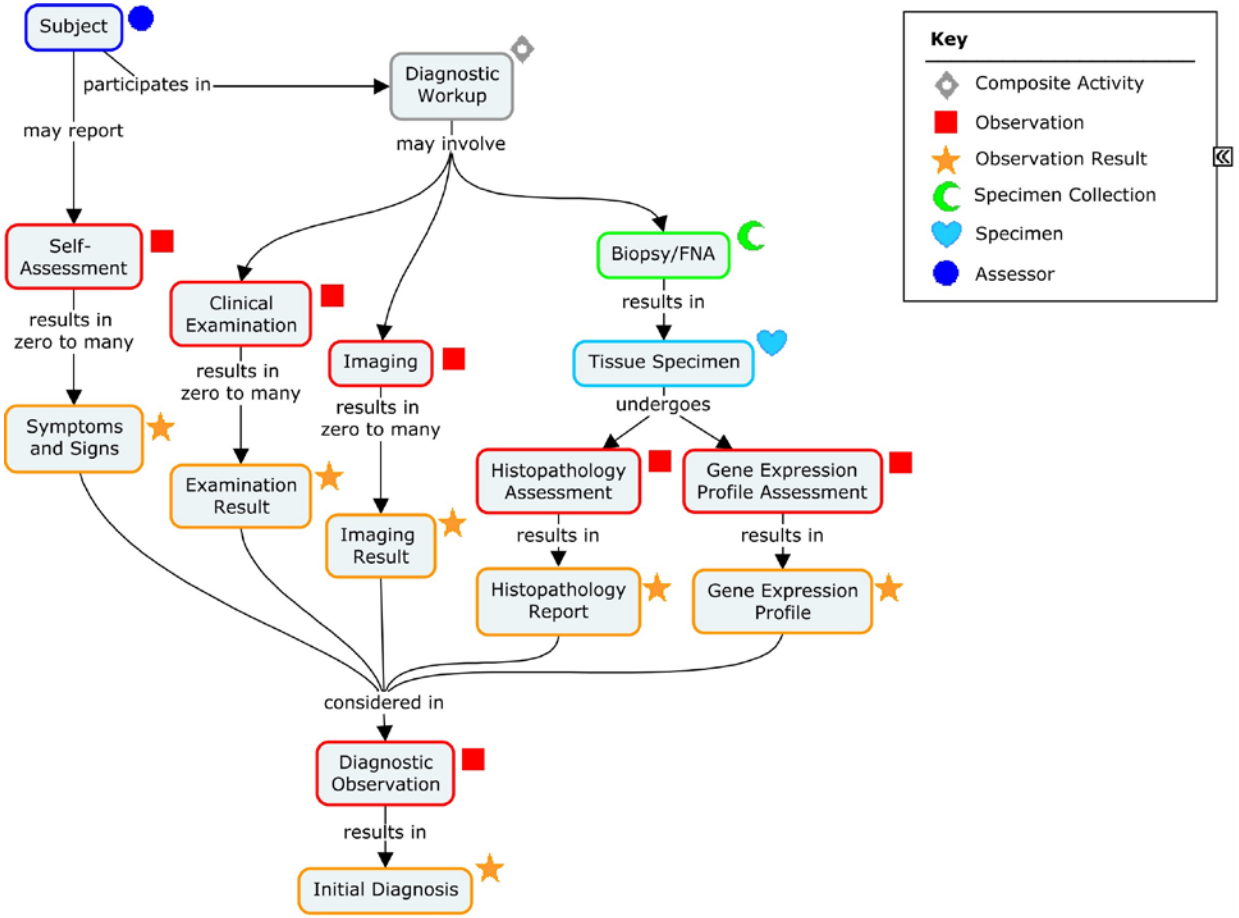
The diagnostic workup of breast cancer at entry into clinical trials is important because the type of breast cancer and associated risk factors influence survival and may affect eligibility. In addition, randomization and analysis may be stratified by risk factors. The type of data collected is influenced by the stage of breast cancer being evaluated in the clinical trial. Generally, studies in advanced breast cancer will collect data both on the initial breast cancer diagnosis and from additional diagnostic workups conducted when the subject enters the study.

Data on breast cancer initial diagnosis includes the age at initial diagnosis and the date of diagnosis. Observations that may contribute to the breast cancer initial diagnosis include:

- Self-assessment (palpation, symptoms of pain, redness, swelling)
- Clinical examinations
- Imaging (mammography, MRI, CT, CT/PET, ultrasound, bone scan; see Section 4.2)
- Fine needle aspiration (FNA), core needle, and/or excisional biopsy (histopathology (cell type and grade), genetic sequencing, gene expression assessment, grading)
- Pathologic assessment (see Section 3.3)

For the purposes of this TAUG, the definition of diagnosis can refer to the following categories:

- Confirmation that breast cancer is present
- Confirmation on the type of breast cancer that is present
- Determination on the severity/extent of the breast cancer



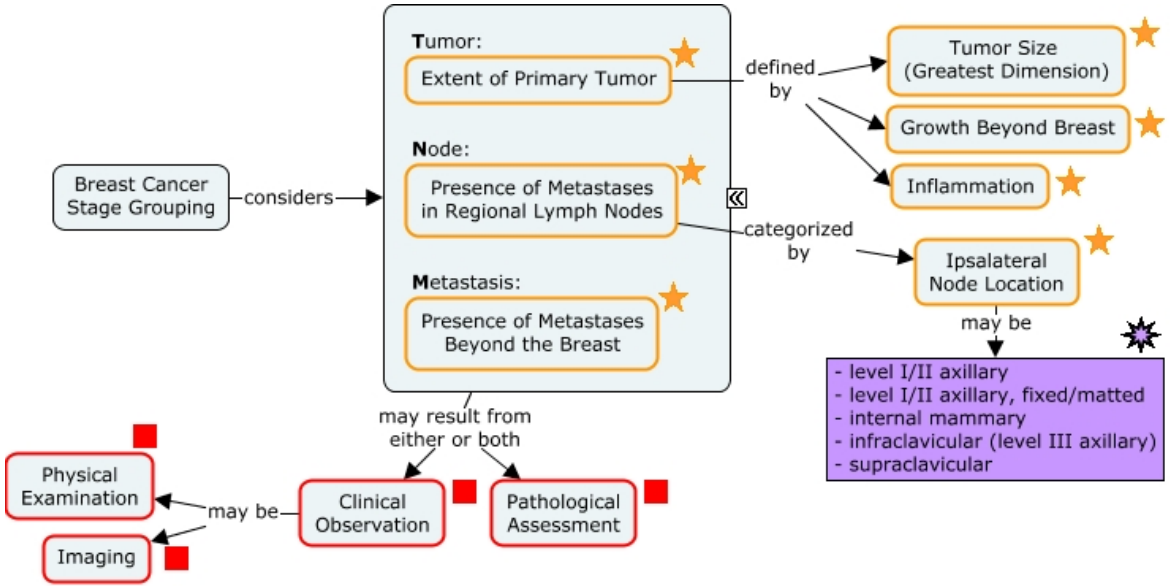
Concept Map 1: Initial Diagnosis of Breast Cancer

3.2 Staging

Disease staging describes the extent to which the malignancy has spread in the body. It contributes to the determination of treatment options and to the estimation of a patient's prognosis. The staging system for breast cancer is described in the American Joint Committee on Cancer (AJCC) Cancer Staging Manual,[6] which uses the Union for International Cancer Control (UICC) TNM Classification.[7]

> The UICC TNM Classification used in breast cancer staging is a named and copyrighted instrument. Guidance on mapping its components to SDTM will be provided as part of a supplement developed by the Questionnaires, Ratings, and Scales (QRS) team, provided that permission to do so is granted by the copyright holder.

T, N, and M stand for primary **tumor**, regional lymph **node**, and distant **metastasis**.[6] The stage of breast cancer can be based on indirect measurements from physical exam and imaging tests (clinical staging), and/or on observations made directly on surgically sampled tissue (pathologic staging). Pathologic staging may provide more accurate information than clinical staging, since it requires the breast tumor mass and nearby lymph nodes to be examined macroscopically and microscopically by a pathologist.

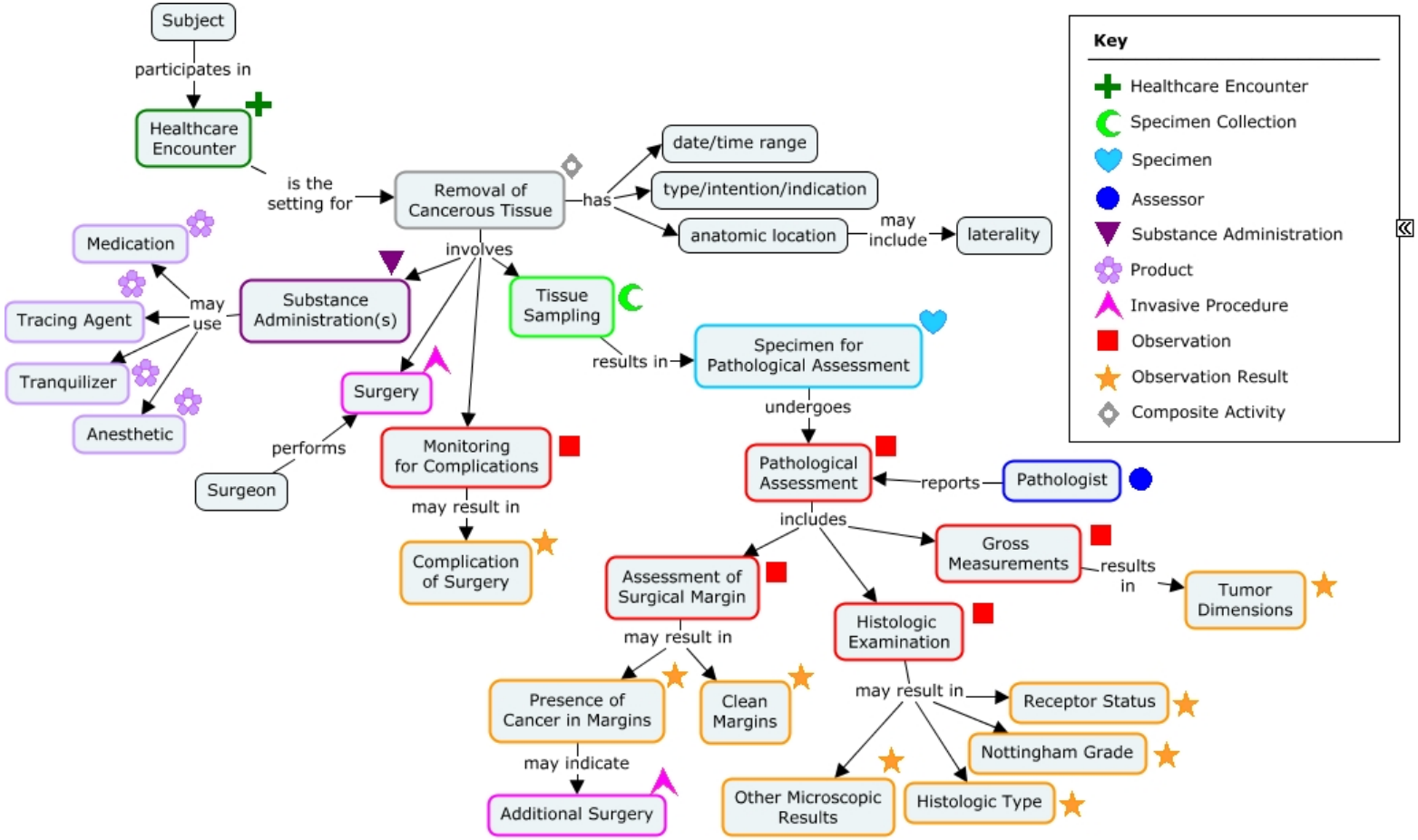


Concept Map 2: Breast Cancer Staging

Concept map is based on the NCI Stage Information for Breast Cancer[8] and the AJCC Cancer Staging Manual.[6] Ipsilateral nodes are nodes on the same side of the body as the tumor.

3.3 Pathology

Following a biopsy or breast surgery, the resected tissue is examined by a pathologist. Pathologic assessments are both macroscopic and microscopic, and provide further detail as to the specific type and aggressiveness of the cancer.



Concept Map 3: Removal of Cancer Tissue

Pathologic assessment of breast cancer includes immunohistochemistry (IHC) assessment for estrogen receptor (ER) and progesterone receptor (PR) as well as IHC or *in situ* hybridization (ISH) determination of human epidermal growth factor receptor 2 (HER2) status.[9] Other testing, such as that for cancer antigens, may be performed as well. Tumors are also graded based on microscopic appearance (e.g., poorly differentiated or well differentiated).[10] Additional genetic

testing of the tumor may occur using a multigene assay or a DNA microarray to assess the risk of disease recurrence, likelihood of development of distant metastases, or to predict responsiveness to systemic therapy. For instance, cDNA microarray analysis of fine needle aspirate in a group of breast cancer patients identified an expression profile of 37 genes, including HMG1 (High Mobility Group Box 1) and COX17 (Cytochrome C Oxidase Copper Chaperone), implicated in good response versus poor response to chemotherapy.[11] The combined pathological data are used to determine cancer aggressiveness, and the risk of recurrence, as well as to guide treatment decisions.

Note that the abbreviations and test names given in the tables in this section are those commonly used in clinical practice. These abbreviations are not necessarily the --TESTCD and --TEST values in CDISC Controlled Terminology. Similarly, the descriptions of these tests are given in the context of breast cancer, and may not be the Controlled Terminology definitions. When constructing standard datasets, consult the current version of CDISC Controlled Terminology (available at: http://www.cancer.gov/cancertopics/cancerlibrary/terminologyresources/cdisc) for values of --TEST and --TESTCD.

The following table lists molecular measurements related to breast cancer. Please note that the following table is not an exhaustive list but details the more common measurements.

Table 3.3.1: Molecular Measurements

Common Test Name (Abbreviation)	Description	
Estrogen Receptor (ER, EsR)	Estrogen receptors belong to the nuclear hormone family of intracellular receptors encoded by the human ESR1 and ESR2 genes. The hormone estrogen and other ligands bind to these receptors to stimulate DNA transcription or cell signaling. Estrogen receptor alpha is the predominant estrogen receptor expressed in breast tissue and is overexpressed in around 50% of breast carcinomas.[12] ER status (positive=present or overexpressed; negative=absent) is a factor in determining prognosis and treatment options. The following details, of an assessment to determine estrogen receptor status, may sometimes be collected.	
	Receptor Positivity	Receptor positivity may be a qualitative or quantitative measure of the percentage of cells that are positive for staining of hormone receptors, such as estrogen receptor and progesterone receptor.
	Receptor Proportion Score (PS)	Receptor proportion score is a qualitative measurement of the proportion of cells that are positive for staining of hormone receptors, such as estrogen receptor and progesterone receptor.
	Receptor Intensity Score (IS)	Receptor intensity score is a qualitative measure of the average staining intensity for hormone receptors, such as estrogen receptor and progesterone receptor.
	Receptor Total Score (TS)	Receptor total score is a computed score that takes into account a combination of the results of the above measures for hormone receptors, such as estrogen receptor and progesterone receptor. These scores can be a factor in determining prognosis and treatment options.
Progesterone Receptor (PR, PgR)	Progesterone receptors belong to the nuclear hormone receptors of the NR3C class and are encoded by the human PGR gene. The hormone progesterone binds to these receptors to stimulate DNA transcription and cell signaling. Progesterone receptor is expressed in 65% of breast carcinomas.[13] PR status (positive=present or overexpressed; negative=absent) is a factor in determining prognosis and treatment options. The following details, of an assessment to determine progesterone receptor status, may sometimes be collected.	
	Receptor Positivity	Receptor positivity may be a qualitative or quantitative measure of the percentage of cells that are positive for staining of hormone receptors, such as estrogen receptor and progesterone receptor.
	Receptor Proportion Score (PS)	Receptor proportion score is a qualitative measurement of the proportion of cells that are positive for staining of hormone receptors, such as estrogen receptor and progesterone receptor.

Common Test Name (Abbreviation)	Description	
	Receptor Intensity Score (IS)	Receptor intensity score is a qualitative measure of the average staining intensity for hormone receptors, such as estrogen receptor and progesterone receptor.
	Receptor Total Score (TS)	Receptor total score is a computed score that takes into account a combination of the results of the above measures for hormone receptors, such as estrogen receptor and progesterone receptor. These scores can be a factor in determining prognosis and treatment options.
Human Epidermal Growth Factor Receptor 2 (HER2, HER2/*neu*)	HER2 is a member of the human epidermal growth factor receptor family of proteins and is encoded by the ERBB2 oncogene. HER2 is overexpressed in 20-30% of breast tumors,[10] and is associated with an aggressive clinical course and poor prognosis. HER2 status (positive=present or overexpressed; negative=absent) is a factor in determining prognosis and treatment options.	
Ki-67 Labeling Index	Ki-67 is a protein phosphatase whose expression is strongly associated with cell proliferation and encoded by the MKI67 gene. The Ki-67 labeling index is the fraction of Ki-67-positive cells to total cells in a tumor specimen and may be useful for determining prognosis with respect to survival and disease recurrence.	

Terms and descriptions in this table were informed by contributions from CFAST membership organizations and by the NCI EVS.

The following table lists cancer measurements related to breast cancer. Please note that the following table is not an exhaustive list but details the more common measurements.

Table 3.3.2: Cancer Measurements

Common Test Name (Abbreviation)	Description
Tumor Size	The size of the tumor, usually given in millimeters. Tumor size may refer to invasive cancer or *in situ* cancer. Pathologists measure the gross tumor in three dimensions. If the tumor is surrounded by normal tissue grossly, then the entire specimen is measured in three dimensions and the actual tumor in two dimensions.
Size of Gross Tumor Bed	The gross tumor bed is the tissue that envelops a tumor site, following the removal of the tumor. This assessment may contribute to the determination of whether neoadjuvant therapy is appropriate, but can be collected for other reasons as well. The measurement of the tumor bed includes at least two dimensions.
Surgical Margin Status	The presence of cancer in the resected tissue surrounding the tumor. Surgical margins can be either clean (clear, negative) or positive. Clean surgical margins indicate that the entire tumor was removed successfully.
Cellularity	A measurement of the degree, quality, or condition of cells in a biological specimen. In terms of cancer, cellularity is the percentage of cells in a specimen that are cancerous. This assessment may contribute to the determination of whether neoadjuvant therapy is appropriate, but can be collected for other reasons as well. Cellularity is a concept that applies to all morphologic variations of cancer.
Percentage of *In Situ* Carcinoma	The percentage of the cancer that is *in situ*, as opposed to invasive.
Size of Largest Lymph Node	The size of the largest lymph node, usually given in millimeters. There is evidence that the presence of large lymph nodes with metastatic breast carcinoma is usually associated with lower overall survival. Note that an axillary lymph node may have metastatic disease regardless of size. For instance, small lymph nodes may have metastases seen microscopically, while large lymph nodes sometimes show reactive follicular hyperplasia but no evidence of metastases.

Common Test Name (Abbreviation)	Description
Lymph Node Status	Indicates whether cancer is present in a lymph node.
Number of Lymph Nodes Positive	The number of lymph nodes (out of those examined) in which cancer was found. More positive lymph nodes are associated with a worse prognosis and the number of positive lymph nodes is a factor in the staging of the cancer.[8]
Size of Largest Lymph Node Metastasis	The longest diameter of the largest lymph node in which cancer was found. One of the parameters used in calculating the residual cancer burden (see below).
Residual Cancer Burden (RCB)	The amount of cancer left after neoadjuvant therapy, as measured by pathologic assessment of the tissue(s) removed at surgery. The residual cancer burden is calculated using the following parameters: primary tumor bed area, *in situ* percentage, cellularity, number of positive lymph nodes, and diameter of largest positive node. The pathologist states the above facts in the pathology report, and whoever calculates the residual cancer burden can easily do so using the established formula.[14] The formula produces a continuous index (RCB Index), which is associated with a qualitative category (RCB Class). The RCB Class is scored from 0 to III, with RCB-0 representing complete pathologic response and RCB-III representing extensive residual disease. The RCB Index can be used as a predictor of distant relapse.[14]

Terms and descriptions in this table were informed by contributions from CFAST membership organizations and by the NCI EVS.

The following table lists primary tumor grade assessments related to breast cancer. Please note that the following table is not an exhaustive list but details the more common assessments.

Table 3.3.3: Primary Tumor Grade Assessments

Common Test Name (Abbreviation)	Description	
Invasive Carcinoma Grade	The degree of abnormality of tumor cells. Grading is a histopathologic finding that is determined from the evaluation of the tubule formation, nuclear pleomorphism, and mitotic count. At present, the most common system is the Nottingham grading system, also called the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system.[6,9,15] The grade of a tumor represents its aggressive potential, with a lower grade being more favorable. It may be used to plan treatment and estimate the future course, outcome, and overall prognosis of disease. The following details of the assessment that determines invasive carcinoma grade may be collected.	
	Tubule Formation	A comparison between the structures formed by the tumor cells as opposed to those formed by normal cells; how much the tumor tissue resembles healthy mammary glands. Scored from 1 to 3, with 1 being the most normal and 3 the most abnormal.
	Nuclear Pleomorphism	How large and varied the nuclei of the tumor cells are. Scored from 1 to 3, with 1 being the least amount of pleomorphism and 3 the most.
	Mitotic Count	How fast the tumor cells are growing and dividing, as determined by the number of mitotic cells present. Also scored from 1 to 3; a higher mitotic count results in a higher score.
	Total Score	Graded from 1 to 3. The sum of the tubule formation, nuclear pleomorphism, and mitotic count scores. It ranges from 3 to 9. A total score of 3-5 is designated as grade 1; 6-7 is grade 2; 8-9 is grade 3.
Ductal Carcinoma *In Situ* Grade (DCIS Grade)	The degree of abnormality of ductal breast carcinoma *in situ*. Higher grade DCIS has a worse prognosis.	

Common Test Name (Abbreviation)	Description
Lobular Carcinoma *In Situ* Grade (LCIS Grade)	The degree of abnormality of lobular breast carcinoma *in situ*.

Terms and descriptions in this table were informed by contributions from CFAST membership organizations and by the NCI EVS.
The table above show examples of some of the most common grading scales. There are other grading scales that might be used depending upon sponsor/protocol requirements.

The findings below may be collected as results of a general microscopic examination looking for abnormalities, or may be collected via individual questions with present/absent responses. Please note that the following table is not an exhaustive list but details the more common types.

Table 3.3.4: Pre-specified Findings

Common Test Name (Abbreviation)	Description
Calcification	Basophilic, granular deposits of inorganic material in tissue. Calcification can be a radiologic, gross, or microscopic pathologic finding. It may or may not indicate the presence of cancer.
Extranodal Extension	The extension of the cancer beyond the lymph node capsule. Sometimes also called “extranodal involvement.”
Lymphatic-Vascular Invasion	The presence of tumor emboli or tumor masses within lymphatic or circulatory vessels. Lymphatic and/or vascular invasion is a microscopic finding, implying that the tumor has metastasized.
Skin Involvement	Breast carcinoma with macroscopic and/or histologic extension to the skin. Macroscopic skin involvement refers to inflammatory breast carcinoma, which is classified as AJCC stage IIIB (T4d) unless other criteria suggest more advanced staging. Histologic skin involvement only refers to non-inflammatory breast carcinoma, which extends to the skin without macroscopic evidence of skin involvement. Non-inflammatory breast carcinomas usually are of lower stage and have a less aggressive clinical course as compared to inflammatory breast carcinomas.

Terms and descriptions in this table were informed by contributions from CFAST membership organizations and by the NCI EVS.

The following table contains genetic and molecular analysis terms related to breast cancer. Please note that the following table is not an exhaustive list but details the more common types.

Table 3.3.5: Genetic/Molecular Analysis

Common Test Name (Abbreviation)	Description
BRCA1 Mutation	*BRCA1* is a tumor suppressor gene.[16] About 5% to 10% of breast cancers are hereditary.[17] Germline (inheritable) mutations in the **Br**east **Ca**ncer **1** early onset (*BRCA1*) gene often result in a truncated form of the protein it encodes (also BRCA1, sometimes called the breast cancer type 1 susceptibility protein). Some mutations are known to be associated with increased breast and ovarian cancer (deleterious). Some variants may be identified on a pathology report but are not yet known to be deleterious.
BRCA2 Mutation	Like *BRCA1*, *BRCA2* is a tumor suppressor gene[16] that encodes a protein responsible for repairing DNA.[18] Germline (inheritable) mutations in the *BRCA2* gene are associated with increased risk of male breast cancer. Single nucleotide substitutions and small deletions or insertions (1–20 bases) account for the majority of mutations in the *BRCA2* gene. Most of these alterations result in a truncated form of the breast cancer type 2 susceptibility protein. Some mutations are known to be associated with increased breast and ovarian cancer (deleterious). Some variants may be identified on a pathology report but are not yet known to be deleterious.

Gene Expression Profile	A gene expression assay that analyzes a specific panel of genes to estimate risk of metastasis/recurrence in early-stage breast cancer, such as Oncotype DX® and MammaPrint®. The reported result is a calculated score and/or category (e.g., low-risk, high-risk) formulated from the degree of over- or under-expression for each individual gene, and may impact treatment decisions and survival expectancies.

Terms and descriptions in this table were informed by contributions from CFAST membership organizations and by the NCI EVS.

Users should refer to the SDTMIG-PGx for information on modeling this type of data, including any Next-Generation Sequencing.

The following table contains diagnostic terms derived from conventional light microscopic examination of the tissues. Please note that the following table is not an exhaustive list but details the more common types.

Table 3.3.6: Histologic/Morphologic/Molecular Types of Breast Cancer

Common Name (Abbreviation)	Description
Ductal Carcinoma *In Situ* (DCIS)	A carcinoma entirely confined to the mammary ducts, with no evidence of invasion of the basement membrane. Also called intraductal carcinoma.
Lobular Carcinoma *In Situ* (LCIS)	An adenocarcinoma entirely confined to the mammary lobules and characterized by a proliferation of monomorphic cells completely filling the lumina. The overall lobular architecture is preserved. LCIS is frequently multifocal (90% in some series) and bilateral. It rarely becomes invasive, but having LCIS in one breast increases the risk of developing invasive cancer in the other breast.
Invasive Carcinoma	A carcinoma that is not confined to the epithelium and has spread to the surrounding stroma. Invasive cancer contrasts with *in situ* cancer, which is confined to the structure in which it originated (see DCIS and LCIS above). Invasive cancer has a worse prognosis than *in situ* cancer.
Adenoid Cystic Carcinoma	A rare carcinoma that usually arises in the salivary glands, or a carcinoma in which cells bear a strong histologic resemblance to tissue belonging to the salivary glands. Adenoid cystic carcinomas spread along nerve sheaths, resulting in severe pain, and they tend to recur. Lymph node metastases are unusual; hematogenous tumor spread is characteristic.
Apocrine Carcinoma	A carcinoma in which more than 90% of the malignant cells show apocrine differentiation. It originates in the sweat glands of the breast. There is no statistical difference in prognosis compared with non-apocrine breast carcinomas.
Basal-Like Breast Cancer (BLBC)	A carcinoma of the breast in which the cells bear histologic resemblance to the basal cells, which are found in the lower part of the epidermis. BLBC tumors account for 50% to 80% of triple-negative breast cancer (cancers that test negative for estrogen receptors (ER-) and progesterone receptors (PR-) and HER2 (HER2-));[19] however, not all BLBCs are triple negative, and not all triple-negative tumors are BLBC.
HER2-Enriched	A biologic subset of breast carcinoma types defined by high expression of HER2, GRB7, and TRAP100, and by the lack of expression of estrogen receptor (ER). [NCI]

Common Name (Abbreviation)	Description
Inflammatory Breast Cancer	An advanced, invasive breast adenocarcinoma characterized by the presence of distinct changes in the overlying skin. These changes include diffuse erythema, edema, *peau d'orange* (skin of an orange) appearance, tenderness, induration, warmth, enlargement, and in some cases a palpable mass. Inflammatory breast cancer is so-called because of its similar presentation to mastitis, but it is not itself an inflammation. The skin changes are the consequence of lymphatic obstruction from the underlying invasive breast adenocarcinoma. Microscopically, the dermal lymphatics show prominent infiltration by malignant cells. The invasive breast adenocarcinoma is usually of ductal NOS type.
Invasive Carcinoma Mixed Ductal and Lobular	An invasive ductal breast carcinoma associated with a lobular carcinomatous component. The lobular carcinomatous component may be *in situ* or invasive.
Invasive Ductal Carcinoma Not Otherwise Specified (NOS)	The most common type of invasive breast carcinoma, accounting for approximately 70% of breast carcinomas. The gross appearance is usually typical with an irregular stellate outline. Microscopically, randomly arranged epithelial elements are seen. When large sheets of malignant cells are present, necrosis may be seen. With adequate tissue sampling, *in situ* carcinoma can be demonstrated in association with the infiltrating carcinoma. The *in situ* component is nearly always ductal but occasionally may be lobular or both.
Invasive Lobular Carcinoma	An invasive adenocarcinoma arising in the lobules of the mammary gland, as opposed to the ducts. The malignant cells lack cohesion and are arranged individually, in a linear manner (Indian files), or as narrow trabeculae within the stroma. The malignant cells are usually smaller than those of ductal carcinoma, are less pleomorphic, and have fewer mitotic figures.
Luminal A	A biologic subset of breast carcinoma defined by high expression of genes characteristic of luminal epithelial cells, including estrogen receptor (ER), estrogen regulated protein (LIV-1), and the transcription factors hepatocyte nuclear factor 3 (HNF3), hepatocyte nuclear factor 3 alpha (HNF3A), X-Box binding protein 1 (XBP1), and GATA binding protein 3 (GATA3). This subtype of breast cancer is associated with a good prognosis. [NCI]
Luminal B	A biologic subset of breast carcinoma defined by low to moderate expression of genes characteristic of luminal epithelial cells including estrogen receptor (ER), and high expression of gamma-glutamyl hydrolase (GGH), lysosomal protein transmembrane 4 beta (LAPTM4B), and Cycline E1 (CCNE1). This subtype of breast cancer is associated with a good prognosis, although not as favorable as the luminal A subtype. [NCI]
Medullary Carcinoma	A rare subtype of invasive ductal carcinoma called “medullary” because the tissue resembles the medulla of the brain. Medullary carcinoma is a less aggressive form of cancer.
Metaplastic Breast Cancer (MBC)	A rare invasive carcinoma showing differentiation toward cartilaginous structures (chondroid metaplasia) or toward bone structures (ossia metaplasia). Data on MBC are limited,[20] and prognostic implications have yet to be fully determined.[21,22]
Mucinous Carcinoma	An invasive adenocarcinoma of the breast characterized by the presence of islands of small and uniform cells, surrounded by large amounts of mucin. Pure mucinous breast carcinomas generally have a favorable prognosis.
Paget's Disease	A malignant neoplasm composed of large cells with large nuclei, prominent nucleoli, and abundant pale cytoplasm (Paget cells). Usually arises in the nipple.
Papillary Carcinoma	A malignant epithelial neoplasm characterized by small finger-like (papillary) growths. Papillary carcinoma can be intraductal or invasive. The intraductal papillary carcinoma in the absence of concomitant DCIS or invasive carcinoma in the surrounding tissues has a favorable prognosis.

Common Name (Abbreviation)	Description
Tubular Breast Cancer	An invasive breast carcinoma comprised of tubular structures lined by a single layer of epithelium. Tubular breast cancer has a favorable prognosis.

Terms and descriptions in this table were informed by contributions from CFAST membership organizations and by the NCI EVS.

3.3.1 Examples for Pathology

Example 1

In this example, IHC for Estrogen Receptor protein expression in a tissue was reported as an overall status, along with details used to determine that overall status. Those details are percentage of cells staining positive, proportion score (PS), stain intensity positivity score (IS), and a total score (TS). This example has been modeled in a fashion consistent with the examples given for the Microscopic Findings (MI) domain in SDTMIG v3.2. For scores that were determined using a multi-point scale, the number of points in the scale was placed in an NSV, PTSCL. Controlled terminology for MITSTDTL is in development.

Row 1: Shows the overall status for estrogen receptor positivity, which was determined from the TS (see Row 5), where TS of >=3 is considered Positive.
Row 2: Shows the percentage of cells that stained positive.
Row 3: Shows PS, which was assigned based on the percentage of positive cells, using a six-point scale.
Row 4: Shows IS, which was scored from 0 to 3, based on the intensity of the scale.
Row 5: Shows the total score, which is the sum of PS and IS.

mi.xpt

Row	STUDYID	DOMAIN	USUBJID	MISEQ	MITESTCD	MITEST	MITSTDTL	MIORRES	MIORRESU	MISTRESC	MISTRESN	MISTRESU
1	ACB	MI	ACB-1201	1	ER	Estrogen Receptor	Overall Status	POSITIVE		POSITIVE		
2	ACB	MI	ACB-1201	2	ER	Estrogen Receptor	Percent Positive Cell	8	%	8	8	%
3	ACB	MI	ACB-1201	3	ER	Estrogen Receptor	Proportion Score	2		2	2	
4	ACB	MI	ACB-1201	4	ER	Estrogen Receptor	Intensity Positivity Score	+2		2	2	
5	ACB	MI	ACB-1201	5	ER	Estrogen Receptor	Total Score	4		4	4	

Row	MISPEC	MILOC	MIMETHOD	MIDRVFL	VISIT	VISITNUM	PTSCL
1 (cont)	TISSUE	BREAST	IHC	Y	SCREENING	10	
2 (cont)	TISSUE	BREAST	IHC		SCREENING	10	
3 (cont)	TISSUE	BREAST	IHC	Y	SCREENING	10	6-Point Scale
4 (cont)	TISSUE	BREAST	IHC		SCREENING	10	4-Point Scale
5 (cont)	TISSUE	BREAST	IHC	Y	SCREENING	10	

Relevant metadata for PTSCL, from the *define.xml* file that would accompany submission, are tabulated below. Note that only those attributes or elements that assist the example have been included. For more information on variable-level metadata in general, see Define-XML v2.0 Sections 4.2 and 5.3.11.

MI NSV Metadata

Variable	Label	Type	Role	Origin
PTSCL	Point Scale	text	Non-Standard Variable Qualifier of MITSTDTL	CRF

See also SDTMIG v3.2, Section 6.3 - MI Domain: Examples 1 and 2.

Example 2
In this example, the subject underwent a lumpectomy at Week 4 that produced a measurable tumor that was assessed by an independent pathologist (see Section 4.1.1, Example 1). This example was modeled in a fashion consistent with Tumor Identification in the TU domain and Tumor Results in the TR domain in SDTMIG v3.2.

Note that TULNKID/TRLNKID is populated to allow linking between TU and TR records and TUREFID/PRREFID/MIREFID is populated to allow linking between TU and the record of the surgery in PR and the record of surgical margin status in MI via RELREC.

Row 1: Shows the tumor was identified as malignant in the pathological sample.

tu.xpt

Row	STUDYID	DOMAIN	USUBJID	TUSEQ	TUREFID	TULNKID	TUTESTCD	TUTEST	TUORRES	TULOC	TULAT	TUEVAL
1	ABC	TU	ABC-1001	1	1001-LT	T01	TUMIDENT	TUMOR IDENTIFICATION	MALIGNANT	BREAST	LEFT	INDEPENDENT ASSESSOR

Row	TUEVALID	TUDTC
1 (cont)	PATHOLOGIST	2014-04-15

Rows 1-2: Shows the longest diameter and longest perpendicular measurements of the tumor in the pathological sample.

tr.xpt

Row	STUDYID	DOMAIN	USUBJID	TRSEQ	TRLNKID	TRTESTCD	TRTEST	TRORRES	TRORRESU	TREVAL
1	ABC	TR	ABC-1001	1	T01	LDIAM	LONGEST DIAMETER	8	mm	INDEPENDENT ASSESSOR
2	ABC	TR	ABC-1001	2	T01	LPREP	LONGEST PERPENDICULAR	3	mm	INDEPENDENT ASSESSOR

Row	TREVALID	TRDTC
1 (cont)	PATHOLOGIST	2014-04-15
2 (cont)	PATHOLOGIST	2014-04-15

The fact that the surgical margins were clean (or negative) is recorded in MI.

mi.xpt

Row	STUDYID	DOMAIN	USUBJID	MISEQ	MIREFID	MITESTCD	MITEST	MIORRES	MISTRESC	MISPEC	MILOC	MIEVAL
1	ABC	MI	ABC-1001	1	1001-T01	SGMGSTAT	Surgical Margins Status	NEGATIVE	NEGATIVE	TISSUE	BREAST	INDEPENDENT ASSESSOR

Row	MIEVALID	MIDTC
1 (cont)	PATHOLOGIST 1	2014-04-15

See Section 4.1.1, Example 1 for the PR records associated with this example, and the RELREC records that relate PR to TU/TR and MI.

3.4 Prior Treatments

If the subjects are not newly diagnosed with breast cancer when they join the study, any prior antineoplastic therapies (i.e., anti-cancer treatments) may be of special interest to the study. Even if subjects are newly diagnosed, it may still be relevant to collect prior treatments for any other cancers they may have had.

3.4.1 Examples for Prior Treatments

Example 1

This is an example of a study where prior antineoplastic medications were collected. The example dataset below shows sample data for two subjects where prior antineoplastic medications were administered. The sponsor has chosen to capture medications by regimen because they expect to perform regimen-based analysis, which can be impacted by the combinations of medications given, and by the setting in which they were given.

Rows 1-2: Subject ABC123-1234 was taking two medications as part of the same regimen (CMGRPID) in a neoadjuvant setting.
Row 3: Subject ABC123-1234 was taking one medication as the second regimen (CMGRPID) in an adjuvant setting.
Row 4: Subject ABC123-2345 was taking one medication as the first regimen (CMGRPID) in an adjuvant setting.
Rows 5-6: Subject ABC123-2345 was taking two medications as part of the second regimen (CMGRPID) in therapeutic-metastatic setting.

cm.xpt

Row	STUDYID	DOMAIN	USUBJID	CMSEQ	CMGRPID	CMTRT	CMDOSE	CMDOSU	CMCAT	CMINDC	CMSTDTC
1	ABC123	CM	ABC123-1234	1	REGIMEN 1	DOXORUBICIN	60	mg/m2	ANTI-CANCER THERAPY	BREAST CANCER	2005-08-15
2	ABC123	CM	ABC123-1234	2	REGIMEN 1	CYCLOPHOSPHAMIDE	600	mg/kg	ANTI-CANCER THERAPY	BREAST CANCER	2005-08-15
3	ABC123	CM	ABC123-1234	3	REGIMEN 2	TAMOXIFEN	20	mg	ANTI-CANCER THERAPY	BREAST CANCER	2006-06-15
4	ABC123	CM	ABC123-2345	1	REGIMEN 1	PACLITAXEL	175	mg/m2	ANTI-CANCER THERAPY	BREAST CANCER	2005-04-04
5	ABC123	CM	ABC123-2345	2	REGIMEN 2	VINFLUNINE	320	mg/m2	ANTI-CANCER THERAPY	BREAST CANCER	2010-03-15
6	ABC123	CM	ABC123-2345	3	REGIMEN 2	GEMCITABINE	1000	mg/m2	ANTI-CANCER THERAPY	BREAST CANCER	2010-03-15

Row	CMENDTC	TRTINT	TRTSTT	RSDISC
1 (cont)	2005-08-23	CURATIVE	NEO-ADJUVANT	COMPLETED PRESCRIBED REGIMEN
2 (cont)	2005-08-23	CURATIVE	NEO-ADJUVANT	COMPLETED PRESCRIBED REGIMEN
3 (cont)	2010-07-01	CURATIVE	ADJUVANT	DISEASE PROGRESSION
4 (cont)	2005-06-06	CURATIVE	ADJUVANT	COMPLETED PRESCRIBED REGIMEN
5 (cont)	2010-08-20	PALLIATIVE	METASTATIC	COMPLETED PRESCRIBED REGIMEN
6 (cont)	2010-08-20	PALLIATIVE	METASTATIC	COMPLETED PRESCRIBED REGIMEN

Variable-level metadata for the NSVs, from the *define.xml* file that would accompany submission, are given in tabulated form below. Note that the "Codelist" column holds the name of the codelist to which the variable refers. Further information about the codelist, including any references to external sources, NCI/CDISC controlled terminology, and/or an enumeration of permissible values, is part of the codelist definition, as opposed to the variable definition.

CM NSV Metadata

Variable	Label	Type	Codelist	Role	Origin
TRTINT	Treatment Intent	text	Treatment Intent	Non-Standard Record Qualifier	CRF
TRTSTT	Setting	text	Treatment Setting	Non-Standard Record Qualifier	CRF
RSDISC	Reason for Discontinuation	text		Non-Standard Record Qualifier	CRF

Example 2

In this example, prior antineoplastic radiotherapies were collected.

Annotated CRF: Radiation Therapy

This CRF is only an example and is not meant to imply that any particular layout is preferable over another.

CRF annotated to show mapping. SDTM variables are in **Red**. If CDASH variable differs from SDTM, the CDASH variable is in **Blue**.
*new variable request submitted. Refer to the corresponding CDASH Metadata table for more information on Sponsor-related Implementation decisions and TA specific usage rules.

Radiation Therapy PRCAT	
Was <Prior/on-treatment/post-treatment> radiation performed? **PRYN**	☐ Yes ☐ No
Radiation Therapy Type: **PRTRT**	☐ 3D Conformal Radiation Therapy ☐ External Beam Radiation Therapy ☐ Intensity-Modulated Radiation Therapy ☐ Brachytherapy, Interstitial ☐ Brachytherapy, Intracavitary ☐ Brachytherapy ☐ High-Dose Rate Brachytherapy ☐ Low-Dose Rate Brachytherapy ☐ Other
Radiation Therapy Type: Other, specify: **PRTRTOTH** **PRTRT**	_____ (A200)
Treatment Intent **PRTRTINT*** **SUPPPR.TRTINT**	☐ Palliative ☐ Curative ☐ Unknown
Setting **PRTRTSTT*** **SUPPPR.TRTSTT**	☐ Adjuvant ☐ Neo-adjuvant ☐ Metastatic ☐ Unknown
Modality Type: **PRTRTDTL*** **SUPPPR.TRTDTL**	☐ Alpha ☐ Electron ☐ Mixed ☐ Neutron ☐ Photon ☐ Proton ☐ Unknown
Radiation Relative Location(s) Category *check all that apply* **PRRRLTLC*** **SUPPPR.RRLTLC**	☐ Primary ☐ Regional ☐ Distant ☐ Unknown

Anatomical Location **PRLOC**	*Pre-specified on CRF or Select list of values from LOC CT* (…) ☐ Other
Anatomical Location: Other, Specify: **PRLOCOTH*** **PRLOC**	(A200)
Laterality **PRLAT**	☐ Left ☐ Right ☐ Bilateral
Start Date: (DD-MMM-YYYY) **PRSTDAT** **PRSTDTC**	_ _ / _ _ _ / _ _ _ _
End Date: (DD-MMM-YYYY) **PRENDAT** **PRENDTC**	_ _ / _ _ _ / _ _ _ _
Dose **PRDOS** **PRDOS or PRDOSTXT**	
Cumulative Dose **PRCMLDOS*** **SUPPPR.CMLDOS**	(N4)
Dose Unit **PRDOSU**	☐ cGy ☐ Gy ☐ Rad ….
Intended Dose Regimen **PRDOSRGM**	(A200)
Total Fractions Count **PRRTTLFR*** **SUPPR.RTTLFR**	(N4)
Best Overall Response: **PRTRTBOR*** **SUPPPR.TRTBOR**	☐ Complete Response ☐ Partial Response ☐ Stable Disease ☐ Progressive Disease ☐ Minimal Response ☐ Symptom Relief ☐ Not Evaluable ☐ Unknown

The example shows data for three subjects where prior antineoplastic radiotherapy was administered. The level of detail for radiation data collection may vary greatly based on disease population. This sponsor narrowed Radiation CRF collection to therapy type, treatment setting, and start and end date. Indication was populated per protocol. The approach for representing PRLOCOTH is available in the SDTM IG and will not be repeated in this TAUG.

Row 1: Subject ABC123-1234 had a prior radiotherapy treatment given to the supraclavicular lymph nodes in an adjuvant setting.
Rows 2-3: Subject ABC123-2345 had two prior radiotherapy treatments: one given to the breast in a neoadjuvant setting, and the other given to the lumbar vertebrae in a metastatic setting.
Row 4: Subject ABC123-2346 had a prior radiotherapy treatment given to the axillary lymph nodes in an adjuvant setting.

pr.xpt

Row	STUDYID	DOMAIN	USUBJID	PRSEQ	PRTRT	PRCAT	PRINDC	PRLOC
1	ABC123	PR	ABC123-1234	1	BRACHYTHERAPY	RADIATION THERAPY	BREAST CANCER	SUPRACLAVICULAR LYMPH NODE
2	ABC123	PR	ABC123-2345	1	EXTERNAL BEAM RADIOTHERAPY	RADIATION THERAPY	BREAST CANCER	BREAST
3	ABC123	PR	ABC123-2345	2	BRACHYTHERAPY	RADIATION THERAPY	BREAST CANCER	LUMBAR VERTEBRA
4	ABC123	PR	ABC123-2346	1	BRACHYTHERAPY	RADIATION THERAPY	BREAST CANCER	AXILLARY LYMPH NODE

Row	VISITNUM	VISIT	PRSTDTC	PRENDTC	TRTSTT
1 (cont)	10	SCREENING	1990-04-15	1990-04-22	ADJUVANT
2 (cont)	10	SCREENING	1998-01-22	1998-02-10	NEO-ADJUVANT
3 (cont)	10	SCREENING	2007-04-30	2007-05-10	METASTATIC
4 (cont)	10	SCREENING	1998-05-30	1998-06-20	ADJUVANT

Relevant metadata for TRTSTT used in the dataset above are given below.

PR NSV Metadata

Variable	Label	Type	Codelist	Role	Origin
TRTSTT	Setting	text	Treatment Setting	Non-Standard Record Qualifier	CRF

3.5 Risk Factors

Major Comorbid Conditions

In the broad population and clinical trials, comorbidities may potentially affect survival and treatment tolerability in patients with malignancies. The following list contains examples of some of the possible comorbidities that may be collected for breast cancer clinical trials.

- Diabetes
- Obesity
- Anemia
- Hypertension
- Cardiovascular diseases
- Cerebrovascular diseases
- Chronic Obstructive Pulmonary Disease (COPD)
- Renal disease
- Liver injury
- Hepatitis B
- Hepatitis C
- Osteoporosis

Family History

Family history of breast and/or ovarian cancer is associated with increased breast cancer risk, and is particularly relevant to chemoprevention trials and risk reduction studies. It is also useful for determining whether additional, more extensive genetic risk assessment (e.g., *BRCA1* or *BRCA2* mutation testing) and counseling should be undertaken.

Information of interest about biological relatives may include:

- Their degree of relationship to the subject
- Whether they had breast or ovarian cancer, and if so,
    - Age at diagnosis
    - If it was bilateral breast cancer

    - If it was male breast cancer
    - If it resulted in death
- If they have known *BRCA1*/*BRCA2* mutations
- If they have other mutations that may be relevant to breast cancer (e.g., Tumor Protein P53 (TP53), phosphatase and tensin homolog (PTEN))

For guidance on representing data about subjects' family members in SDTM-based domains, see the SDTM Implementation Guide for Associated Persons (SDTMIG-AP).

4 Disease Management and Assessments

The management of breast cancer depends on tumor histology and characteristics, axial lymph node status, receptor status, presence or absence of metastatic disease, results of multigene panel testing, and patient factors (e.g., age, menopausal status, comorbid conditions), including the patient's preference for treatment, especially if the predicted survival benefits are equivalent for different treatment options. In the context of clinical trials, treatment can be categorized according to **intent** and **setting**.

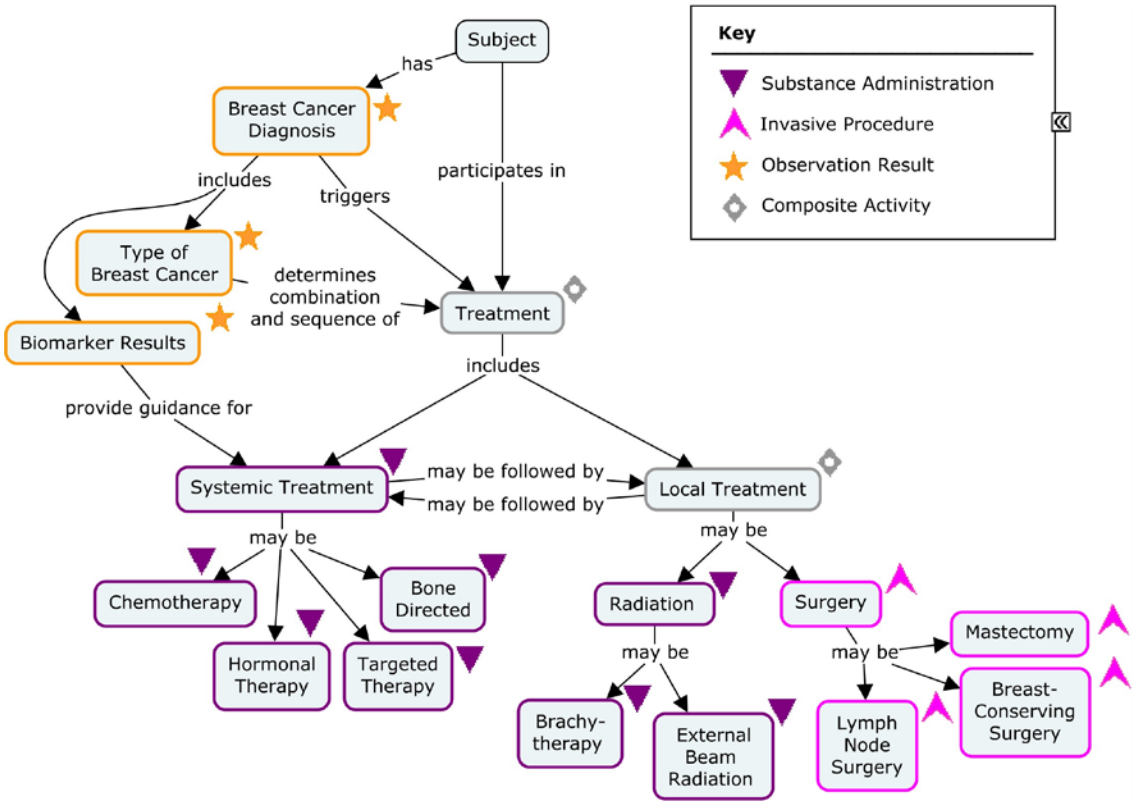
A treatment's intent is the best kind of effect it could be expected to have on the disease. Treatments with **curative** intent ultimately hope to completely destroy the cancer and prevent its recurrence. Treatments with **palliative** intent are typically given when the condition is incurable, and aim instead to halt the progression of the disease and/or improve the patient's quality of life.

The setting describes the treatment's purpose in relation to the primary treatment, which for cancer is the surgical removal of the cancerous tissue. Treatment given in the **neoadjuvant** setting is administered prior to surgery in the hopes of mitigating the cancer, potentially eliminating the tumor prior to surgery. Treatment given in the **adjuvant** setting is administered after surgery, with the primary goal of destroying any remaining cancer and preventing recurrence. Both neoadjuvant and adjuvant therapies, therefore, are given with curative intent. The **advanced/metastatic** setting is associated with Stage IV cancer, when surgery may be inapplicable or inadvisable. Advanced therapies are given with palliative intent.

In general, study treatments are assessed with regard to one setting/intent at a time, though success in one area may prompt investigation into its potential efficacy in other settings.

4.1 Treatments

Ways of dealing with breast cancer include cutting it out, trying to destroy it, trying to inhibit it, and ameliorating its effects. Some treatments target only the anatomic region in which the cancer exists; others operate on a systemic level. In general, types of treatments are sequential, instead of concurrent.



Concept Map 4: Treatment of Breast Cancer

Systemic Treatments

- **Chemotherapy** attempts to eradicate cancer by killing fast-growing cells in the body.[23]
- **Hormone therapies** that inhibit the estrogen receptor pathway are a standard part of therapy for tumors that express the estrogen receptor (ER) and/or progesterone receptor (PR).
- **Targeted therapy** consists of a small molecule or monoclonal antibody that acts at the molecular level to interfere with a biological process within the cancer cell or tumor or to strengthen the immune response to the tumor. Targeted therapies are used when appropriate, based on the subtype of breast cancer and staging.

- **Bone-directed therapies** strengthen the bones and help reduce the risk of problems arising from bone metastases.[24]

Local Treatments

- **Radiation therapy** destroys the genetic material in a cell that controls how it grows and divides.[25] It is commonly given following surgery. Sometimes it is considered to be part of the primary therapy; sometimes, adjuvant therapy.
- **Surgery** prevents (or greatly reduces) the spread of cancer by removing the cancerous tissue from the body. The excised, or resected, tissue is then available as a specimen for further study.

  Studies involving subjects with breast cancer may collect data about surgical procedures such as biopsies, dissections, lumpectomies, mastectomies or further surgical interventions. In these studies, the procedure details, including procedure type/intention, date/time, and anatomic location, will often be collected. Data collection may also include location laterality, operative conditions/procedures, tracing-agent administration, surgical findings, and/or gross evidence of tumor(s). For further information about breast cancer surgical procedure types, see the NCCN Guidelines for Breast Cancer at http://www.nccn.org.

4.1.1 Examples for Treatments

Studies may allow specific concomitant palliative cancer treatments. Additionally, after the study treatment is discontinued, sponsors may collect the subsequent cancer therapies given to the subject. All of these cancer therapies are reported in the CM or PR domain in SDTM, while the actual study treatment is represented in the Exposure (EC/EX) domains. See also Section 3.4.1 for examples of prior treatments.

Example 1

In this example, subject ABC-1001 undergoes a lumpectomy/partial mastectomy, which results in a measurable tumor sample (see Section 3.3.1, Example 2). Subject ABC-1002 has an axillary lymph node dissection. This example shows how to represent location of surgery when tissue is excised from a single anatomical location or from multiple locations.

These procedures are represented in the Procedures (PR) domain. The reason for performing them is represented using an NSV.

Row 1: Shows subject ABC-1001's lumpectomy. Note that PRREFID has been populated, which allowed findings from this specimen to be linked to this procedure record. RELREC (given below), shows that the related record(s) are in the TU and TR domains.

Row 2: Shows subject ABC-1002's node dissection. Because lymph nodes were removed from both levels I and II, PRLOC is MULTIPLE and the two locations are given as NSVs.

pr.xpt

Row	STUDYID	DOMAIN	USUBJID	PRSEQ	PRREFID	PRTRT	PRLOC	PRLAT	PRSTDTC	TRTINT	PRLOC1	PRLOC2
1	ABC	PR	ABC-1001	1	1001-T01	LUMPECTOMY/ PARTIAL MASTECTOMY	BREAST	LEFT	2014-04-15	CURATIVE		
2	ABC	PR	ABC-1002	1		NODE DISSECTION	MULTIPLE	RIGHT	2014-04-15		AXILLARY LYMPH NODE LEVEL I	AXILLARY LYMPH NODE LEVEL II

Variable-level metadata for the NSVs, from the *define.xml* file that would accompany submission, are given in tabulated form below. As in Section 3.4.1 Example 1, the "Codelist" column holds the name of the codelist to which the variable refers.

PR NSV Metadata

Variable	Label	Type	Codelist	Role	Origin
TRTINT	Treatment Intent	text	Treatment Intent	Non-Standard Record Qualifier	CRF
PRLOC1	Procedure Location 1	text	Anatomical Location	Non-Standard Record Qualifier	CRF
PRLOC2	Procedure Location 2	text	Anatomical Location	Non-Standard Record Qualifier	CRF

relrec.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
1	ABC	PR		PRREFID		ONE	PRTR
2	ABC	TR		TRREFID		MANY	PRTR
3	ABC	MI		MIREFID		MANY	PRMI
4	ABC	TU		TUREFID		ONE	PRTU

Example 2

This example shows how to handle representation of radiation given on different types of schedules.

Row 1: Represents administration of external beam radiation to the right breast, given each weekday over a period of 25 days. The intended schedule is represented in PRDOSRGM, as this cannot be expressed as a frequency.

Row 2: Represents brachytherapy administered to the left breast on a single occasion.

Row 3: Represents radiation to bone, given once a day for three days.

pr.xpt

Row	STUDYID	DOMAIN	USUBJID	PRSEQ	PRTRT	PRDOSE	PRDOSU	PRDOSFRQ	PRDOSRGM	PRLOC	PRLAT	PRSTDTC	PRENDTC
1	ABC123	PR	ABC123-1001	1	External beam radiation therapy	70	Gy		EACH WEEKDAY	BREAST	RIGHT	2011-06-01	2011-06-25
2	ABC123	PR	ABC123-2002	1	Brachytherapy	25	Gy	ONCE		BREAST	LEFT	2011-07-15	2011-07-15
3	ABC123	PR	ABC123-3003	1	Radiotherapy	300	cGy	QD		BONE		2011-08-19	2011-08-21

4.1.2 Treatment Side Effects

For many cancer treatments, one of the aims of early development is the characterization of side effects, including the identification of dose-limiting toxicities. This aspect of breast cancer study data is beyond the scope of this version of the TAUG-BrCa.

In later development, adverse events that have been found to be associated with a drug will be a focus of data collection and analysis. Data collection will depend on the particular side effects, and varies considerably among breast cancer treatments, so is not covered here. Advice for analysis of adverse events within ADaM structure can be found at: http://www.cdisc.org/adam.

In studies of advanced breast cancer, subjects may have received many prior treatments. Those treatments may include those with known cardiotoxicities, such as anthracyclines. Cardiotoxicity is associated with cumulative lifetime exposure to these drugs, so it may be important to capture prior and ongoing exposure to

these drugs. For patients with prior or ongoing exposure to drugs with cardiotoxicity, studies may include cardiac safety assessments. Assessments such as echocardiograms are not covered in this document, but are expected to be covered by a future TAUG for cardiac imaging.

Examples of therapeutics relevant to breast cancer associated with cardiotoxicity include the following:[26]

Agent	Cardiotoxicity
Anthracyclines and anthraquinones	Congestive heart failure, left ventricular dysfunction, acute myocarditis, arrhythmia
Capecitabine, 5-fluorouracil	Ischemia, pericarditis, congestive heart failure, cardiogenic shock
Paclitaxel, vinca alkaloids	Sinus bradycardia, ventricular tachycardia, atrioventricular block, hypotension, congestive heart failure, ischemia
Cyclophosphamide	Neurohumoral activation, mitral regurgitation
Trastuzumab	Arrhythmias, congestive heart failure, angioedema, left ventricular dysfunction
Bevacizumab	Hypertension, thromboembolism, bleeding
Thorax irradiation	Myocardial fibrosis, valvular heart disease, left ventricular dysfunction

4.2 Tumor Identification, Assessment, and Disease Response

General guidance on managing data pertaining to the identification, monitoring, and assessment of tumors and lesions is covered by three SDTMIG Findings domains: Tumor Identification (TU), Tumor Results (TR), and Disease Response (RS). Please consult SDTMIG v3.2 for specifications, assumptions, and some examples for these domain models.

Two more SDTM-based data examples and an example CRF in three parts relating to Tumor Identification and one CRF relating to Tumor Response are given on the following pages.

4.2.1 Examples for Tumor Identification and Assessment

The example CRFs on the following pages are intended to go with the example datasets in this section. This TAUG illustrates creating a separate CRF for each tumor type classified by the response criteria (i.e., a CRF for Target Lesion, a CRF for Non-Target Lesion, and a CRF for New Lesion).

There are several valid ways in which sponsors capture baseline and post-baseline tumor information, depending on the clinical database system. Many sponsors use a single form, displaying the relevant questions according to the visits using dynamics. The example CRFs in this TAUG reflect this database build option. Other sponsors devise rules to automatically move identifier information gathered at the screening/baseline visit into the proper post-baseline results forms. Others create two separate forms: one for screening/baseline tumor identification and another for post-baseline visits tumor results. For post-baseline visits, Tumor Result CRF(s) and Disease Response CRF(s) are generally presented together. Any of these strategies is an acceptable deployment approach. TULNKID and TRLNKID variables are used to provide a unique code for each identified tumor in order to link records across related domains (TU and TR). TULNKID and TRLNKID are expected to be the same for the same tumor across datasets.

Annotated CRF: Tumor Identification/Results Target Lesions

This CRF is only an example and is not meant to imply that any particular layout is preferable over another.

CRF annotated to show mapping. SDTM variables are in **Red**. If CDASH variable differs from SDTM, the CDASH variable is in **Blue**. *new variable request submitted. Refer to the corresponding CDASH Metadata table for more information on Sponsor-related Implementation decisions and TA specific usage rules.

Target TUTESTCD=TUMIDENT and TUORRES=TARGET

Response Criteria: *Pre-specified*	**RECIST 1.1**
Were tumors identified? **TUYN***	☐ Yes ☐ No
Tumor ID: **TULNKID**	_____ (A10 or Sponsor-Defined CT)
Location: **TULOC**	*<Select appropriate values from LOC CT>*
Laterality: **TULAT**	☐ Left ☐ Right ☐ Bilateral *<Select appropriate values from LAT CT>*
Directionality: **TUDIR**	☐ Distal ☐ Intermediate ☐ Proximal ☐ Inner ☐ Outer *<Select appropriate values from DIR CT>*
Location Detail: **TULOCDTL*** **SUPPTU.LOCDTL**	_____ (A200)
Changes to Tumor Identified: **TUCHANGE***	☐ Split **TUTESTCD=TUSPLIT** ☐ Merged **TUTESTCD=TUMERGE**
Method of Evaluation: **TUMETHOD**	☐ Clinical Exam ☐ CT Scan ☐ Ductography ☐ DXA Scan ☐ Echocardiogram ☐ Endoscopy ☐ Mammography ☐ MRI ☐ MUGA ☐ PET Scan ☐ PET/CT Scan ☐ PET/MRI Scan ☐ Photography ☐ Physical Examination ☐ Scintigraphy ☐ Ultrasound ☐ X-Ray *<Select appropriate values from METHOD CT>*
Date of Evaluation: (DD-MMM-YYYY) **TUDAT*** **TUDTC**	_ _ / _ _ _ / _ _ _ _
Evaluator **TUEVAL**	☐ Investigator ☐ Independent Assessor
Evaluator Identifier: **TUEVALID**	☐ Radiologist 1 ☐ Radiologist 2 ☐ Radiologist 3 …
Diameter: **TRTESTCD=DIAMETER** **TRORRES**	_____
Diameter Unit: **TRDIAMU*** **TRORRESU**	**mm**
Diameter Too Small to Measure: **TRTOOSM*** **TRORRES**	☐ Yes

Tumor Inevaluable? **TRINEVAL*** **TRTESTCD=TUMSTATE** **TRSTAT=NOT DONE**	☐ Inevaluable
If Tumor Is Inevaluable, Reason Not Done: **TRREASND**	☐ Lesion or Background Change that Prevents Evaluation ☐ Focal Intervention ☐ Poor Scan Quality ☐ Insufficient Images/Anatomy ☐ Inconsistent Modality ☐ Site Error ☐ Other
Lymph Node State: **TRLNSTAT*** **TRTESTCD=LNSTATE** **TRORRES**	☐ Pathological ☐ Non-Pathological

Annotated CRF: Tumor Identification/Results Non-Target Lesions

This CRF is only an example and is not meant to imply that any particular layout is preferable over another.

CRF annotated to show mapping. SDTM variables are in **Red**. If CDASH variable differs from SDTM, the CDASH variable is in **Blue**.
*new variable request submitted. Refer to the corresponding CDASH Metadata table for more information on Sponsor-related Implementation decisions and TA specific usage rules.

Non-target **TUTESTCD=TUMIDENT and TUORRES=NON-TARGET**

Response Criteria: *Pre-specified*	**RECIST 1.1**
Were tumors identified? **TUYN***	☐ Yes ☐ No
Tumor ID: **TULNKID**	_____ (A10 or Sponsor-Defined CT)
Location: **TULOC**	*<Select appropriate values from LOC CT>*
Laterality: **TULAT**	☐ Left ☐ Right ☐ Bilateral *<Select appropriate values from LAT CT>*
Directionality: **TUDIR**	☐ Distal ☐ Intermediate ☐ Proximal ☐ Inner ☐ Outer *<Select appropriate values from DIR CT>*
Location Detail: **TULOCDTL*** **SUPPTU.LOCDTL**	_____ (A200)
Tumor or Lesion Presentation Type **TUPRTYP** **SUPPTU.PRTYP**	☐ Ascites ☐ Effusion ☐ Leptomeningeal Disease ☐ Simple Cystic ☐ Complex Cystic
Changes to Tumor Identified: **TUCHANGE***	☐ Split **TUTESTCD=TUSPLIT** ☐ Merged **TUTESTCD=TUMERGE**
Method of Evaluation: **TUMETHOD**	☐ Clinical Exam ☐ CT Scan ☐ Ductography ☐ DXA Scan ☐ Echocardiogram ☐ Endoscopy ☐ Mammography ☐ MRI ☐ MUGA ☐ PET Scan ☐ PET/CT Scan ☐ PET/MRI Scan ☐ Photography

	☐ Physical Examination ☐ Scintigraphy ☐ Ultrasound ☐ X-Ray <*Select appropriate values from METHOD CT*>
Date of Evaluation: (DD-MMM-YYYY) **TUDAT*** **TUDTC**	_ _ / _ _ _ / _ _ _ _
Evaluator **TUEVAL**	☐ Investigator ☐ Independent Assessor
Evaluator Identifier: **TUEVALID**	☐ Radiologist 1 ☐ Radiologist 2 ☐ Radiologist 3 …
Tumor State: **TUMSTATE*** **TRTESTCD=TUMSTATE** **TRORRES**	☐ Present ☐ Absent ☐ Present without Unequivocal Progression ☐ Unequivocal Progression
Diameter: **TRTESTCD=DIAMETER** **TRORRES**	_____
Diameter Unit: **TRDIAMU*** **TRORRESU**	**mm**
Diameter Too Small to Measure: **TRTOOSM*** **TRORRES**	☐ Yes
Tumor Inevaluable? **TRINEVAL*** **TRTESTCD=TUMSTATE** **TRSTAT=NOT DONE**	☐ Inevaluable
If Tumor Is Inevaluable, Reason Not Done: **TRREASND**	☐ Lesion or Background Change that Prevents Evaluation ☐ Focal Intervention ☐ Poor Scan Quality ☐ Insufficient Images/Anatomy ☐ Inconsistent Modality ☐ Site Error ☐ Other
Lymph Node State: **TRLNSTAT*** **TRTESTCD=LNSTATE** **TRORRES**	☐ Pathological ☐ Non-Pathological

Annotated CRF: Tumor Identification/Results New Lesions

This CRF is only an example and is not meant to imply that any particular layout is preferable over another.

CRF annotated to show mapping. SDTM variables are in **Red**. If CDASH variable differs from SDTM, the CDASH variable is in **Blue**.
*new variable request submitted. Refer to the corresponding CDASH Metadata table for more information on Sponsor-related Implementation decisions and TA specific usage rules.

New **TUTESTCD=TUMIDENT and TUORRES=NEW**

Response Criteria: *Pre-specified*	**RECIST 1.1**
Were tumors identified? **TUYN***	☐ Yes ☐ No
Tumor ID: **TULNKID**	_____ (A10 or Sponsor-Defined CT)
Location: **TULOC**	<*Select appropriate values from LOC CT*>
Laterality: **TULAT**	☐ Left ☐ Right ☐ Bilateral <*Select appropriate values from LAT CT*>
Directionality: **TUDIR**	☐ Distal ☐ Intermediate ☐ Proximal ☐ Inner ☐ Outer <*Select appropriate values from DIR CT*>

Location Detail: **TULOCDTL*** **SUPPTU.LOCDTL**	(A200)
Tumor or Lesion Presentation Type **TUPRTYP**	☐ Ascites ☐ Effusion ☐ Leptomeningeal Disease ☐ Simple Cystic ☐ Complex Cystic
Method of Evaluation: **TUMETHOD**	☐ Clinical Exam ☐ CT Scan ☐ Ductography ☐ DXA Scan ☐ Echocardiogram ☐ Endoscopy ☐ Mammography ☐ MRI ☐ MUGA ☐ PET Scan ☐ PET/CT Scan ☐ PET/MRI Scan ☐ Photography ☐ Physical Examination ☐ Scintigraphy ☐ Ultrasound ☐ X-Ray *<Select appropriate values from METHOD CT>*
Date of Evaluation: (DD-MMM-YYYY) **TUDAT*** **TUDTC**	_ _ / _ _ _ / _ _ _ _
Evaluator **TUEVAL**	☐ Investigator ☐ Independent Assessor
Evaluator Identifier: **TUEVALID**	☐ Radiologist 1 ☐ Radiologist 2 ☐ Radiologist 3 …
Tumor State: **TUMSTATE*** **TRTESTCD=TUMSTATE** **TRORRES**	☐ Equivocal ☐ Unequivocal Progression ☐ Absent
Diameter: **TRTESTCD=DIAMETER** **TRORRES**	
Diameter Unit: **TRDIAMU*** **TRORRESU**	**mm**
Diameter Too Small to Measure: **TRTOOSM*** **TRORRES**	☐ Yes
Lymph Node State: **TRLNSTAT*** **TRTESTCD=LNSTATE** **TRORRES**	☐ Pathological ☐ Non-Pathological

Annotated CRF: Disease Response

This CRF is only an example and is not meant to imply that any particular layout is preferable over another.

CRF annotated to show mapping. SDTM variables are in **Red**. If CDASH variable differs from SDTM, the CDASH variable is in **Blue**. *new variable request submitted. Refer to the corresponding CDASH Metadata table for more information on Sponsor-related Implementation decisions and TA specific usage rules.

Response Criteria: *Pre-specified* **RSCAT**	**RECIST 1.1**
Was the response assessment performed? **RSYN**	☐ Yes ☐ No **RSSTAT=NOT DONE where RSTESTCD=OVRLRESP**
Reason Response Assessment Not Performed: **RSREASND*** **RSREASND where RSTESTCD=OVRLRESP**	☐ Not Imaged ☐ Patient Refusal ☐ Site Error ☐ Other
Evaluator **RSEVAL**	☐ Investigator ☐ Independent Assessor
Evaluator Identifier: **RSEVALID**	☐ Radiologist 1 ☐ Radiologist 2 ☐ Radiologist 3
Overall Response: **OVRLRESP*** **RSTESTCD=OVRLRESP** **RSTEST=Overall Response**	**RSORRES (RSSTRESC)** ☐ Complete Response (CR) ☐ Partial Response (PR) ☐ Stable Disease (SD) ☐ Non Complete Response/Non Progressive Disease (NON-CR/NON-PD) ☐ Progressive Disease (PD) ☐ Not Evaluable (NE)
Date of Procedure for Overall Response (e.g., scan date): (DD-MMM-YYYY) **OVRLDAT*** **RSDTC**	_ _ / _ _ _ / _ _ _ _
Target Response: **TRGRESP*** **RSTESTCD=TRGRESP** **RSTEST=Target Response**	**RSORRES (RSSTRESC)** ☐ Complete Response (CR) ☐ Partial Response (PR) ☐ Stable Disease (SD) ☐ Progressive Disease (PD) ☐ Not Evaluable (NE) ☐ Not All Evaluated
Date of Procedure for Target Response (e.g., scan date): (DD-MMM-YYYY) **TRGDAT*** **RSDTC**	_ _ / _ _ _ / _ _ _ _
Non-target Response: **NTRGRESP*** **RSTESTCD=NTRGRESP** **RSTEST=Non-target Response**	**RSORRES (RSSTRESC)** ☐ Complete Response (CR) ☐ Non Complete Response/Non Progressive Disease (NON-CR/NON-PD) ☐ Progressive Disease (PD) ☐ Not Evaluable (NE) ☐ Not All Evaluated
Date of Procedure for Non-target Response (e.g., scan date): (DD-MMM-YYYY) **NTRGDAT*** **RSDTC**	_ _ / _ _ _ / _ _ _ _
Best Overall Response: **BESTRESP*** **RSTESTCD=BESTRESP** **RSTEST=Best Overall Response**	**RSORRES (RSSTRESC)** ☐ Complete Response (CR) ☐ Partial Response (PR) ☐ Stable Disease (SD) ☐ Non Complete Response/Non Progressive Disease (NON-CR/NON-PD) ☐ Progressive Disease (PD) ☐ Not Evaluable (NE)
Date of Procedure for Best Overall Response (e.g., scan date): (DD-MMM-YYYY) **BESTDAT*** **RSDTC**	_ _ / _ _ _ / _ _ _ _
Symptomatic Deterioration: SYMPTDTR* **RSTESTCD=SYMPTDTR*** **RSTEST=Symptomatic Deterioration***	**RSORRES (RSSTRESC)** ☐ Yes ☐ No

Date of Symptomatic Deterioration: (DD-MMM-YYYY) **SYMPTDAT*** **RSDTC**	_ _ / _ _ _ / _ _ _ _

Note that the submission value NON-CR/NON-PD follows the proposed controlled terminology due for release in P27

Example 1
This is an example of how data regarding tumor identification via imaging performed at screening might be represented.

In a Findings domain record, --METHOD and --DTC are often enough to identify an imaging procedure. If additional procedure information needs to be captured, then the sponsor may choose to create a separate, related PR record.

In this example, the sponsor has chosen to represent the imaging procedure information using the Procedure (PR) domain.

Row 1: For Subject ABC123-1234, a required Chest X-Ray was acquired on 15APR2014. The Chest X-Ray was pre-specified on the CRF with Yes/No check boxes.
Rows 2-4: For Subject ABC123-2345, a CT scan was acquired on 30MAY2014. The scan covered the chest, abdomen, and pelvis. The imaging was not pre-specified on the CRF.

pr.xpt

Row	STUDYID	DOMAIN	USUBJID	PRSEQ	PRREFID	PRSPID	PRTRT	PRPRESP	PROCCUR	PRLOC	VISITNUM	VISIT	PRSTDTC
1	ABC123	PR	ABC123-1234	1	0124578	1	X-RAY	Y	Y	CHEST	10	SCREENING	2014-04-15
2	ABC123	PR	ABC123-2345	1	6587466_1		CT SCAN			CHEST	10	SCREENING	2014-05-30
3	ABC123	PR	ABC123-2345	2	6587466_2		CT SCAN			ABDOMINAL CAVITY	10	SCREENING	2014-05-30
4	ABC123	PR	ABC123-2345	3	6587466_3		CT SCAN			PELVIS	10	SCREENING	2014-05-30

Any tumors or lesions identified by examining the images produced are included in the Tumor Identification (TU) domain. Note that TU only holds the identification data for each tumor or lesion; tumor results are held in the Tumor Results (TR) domain.

Row 1: Shows the tumor identified for Subject ABC123-1234.
Rows 2 and 4: Show a target tumor and a non-target tumor identified for Subject ABC123-2345.
Row 3: Subject ABC123-2345's screening visit also identified a pleural effusion. The effusion may or may not be malignant, but RECIST criteria are geared toward assessing solid tumors, and an effusion is excess fluid. Therefore, it was marked as non-target.

tu.xpt

Row	STUDYID	DOMAIN	USUBJID	TUSEQ	TUREFID	TULNKID	TUTESTCD	TUTEST	TUORRES	TUSTRESC	TULOC	TULAT
1	ABC123	TU	ABC123-1234	1	0124578	T01	TUMIDENT	Tumor Identification	TARGET	TARGET	BREAST	RIGHT
2	ABC123	TU	ABC123-2345	1	6587466_1	T01	TUMIDENT	Tumor Identification	TARGET	TARGET	BREAST	LEFT
3	ABC123	TU	ABC123-2345	2	6587466_1	NT01	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	PLEURAL CAVITY	
4	ABC123	TU	ABC123-2345	3	6587466_1	NT02	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	BREAST	RIGHT

Row	TUMETHOD	TUEVAL	TUEVALID	VISITNUM	VISIT	TUDTC	PRTYP
1 (cont)	X-RAY	INDEPENDENT ASSESSOR	RADIOLOGIST	10	SCREENING	2014-04-15	
2 (cont)	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	10	SCREENING	2014-05-30	
3 (cont)	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	10	SCREENING	2014-05-30	EFFUSION
4 (cont)	CT SCAN	INDEPENDENT ASSESSOR	RADIOLOGIST	10	SCREENING	2014-05-30	

Relevant metadata for PRTYP, from the *define.xml* file that would accompany submission, are given in tabulated form below. Note that only those attributes or elements that assist the example have been included. For more information on variable-level metadata in general, see Define-XML v2.0 Sections 4.2 and 5.3.11.

Please refer to the CDASH Metadata tables for information on other NSVs referenced in the CRF, as well as more information on data collection for tumors.

TU NSV Metadata

Variable	Label	Type	Role	Origin
PRTYP	Tumor or Lesion Presentation Type	text	Non-Standard Record Qualifier	CRF

Since there are records in PR for the procedure that produced the images used to obtain the findings in TU, RELREC is used to relate these records to each other. In this example, the sponsor has decided to use --REFID consistently across domains, so the relationship can be made at the dataset level.

relrec.xpt

Row	STUDYID	DOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
1	ABC123	PR		PRREFID		ONE	A
2	ABC123	TU		TUREFID		MANY	A

Example 2

This example is for a trial in a metastatic setting where the subjects have sites of disease at baseline. The sample data and modeling are from SDTM Examples for Oncology Use Cases (available at: http://wiki.cdisc.org/x/5yuyAQ), Example 14.

In this example, the subject has one target lesion and two non-target lesions. The target lesion is in the liver. One of the non-target lesions is in the bone, and the other is in the pleural cavity. The lesion in the pleural cavity is an effusion, which is also its most distinguishing characteristic. Therefore, the non-standard variable PRTYP (Tumor Presentation Type), which is intended for use in distinguishing non-measurable lesions in more detail than the combination of the standard location variables can provide, has been populated with "EFFUSION."

tu.xpt

Row	STUDYID	DOMAIN	USUBJID	TUSEQ	TUREFID	TULNKID	TUTESTCD	TUTEST	TUORRES	TUSTRESC	TULOC
1	VWX7777	TU	VWX7777-90000	1	IMG-00001	T01	TUMIDENT	Tumor Identification	TARGET	TARGET	LIVER
2	VWX7777	TU	VWX7777-90000	2	IMG-00002	NT01	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	BONE
3	VWX7777	TU	VWX7777-90000	3	IMG-00001	NT02	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	PLEURAL CAVITY

Row	TUMETHOD	TUEVAL	EPOCH	VISITNUM	VISIT	TUDTC	TUDY	PRTYP
1 (cont)	CT SCAN	INVESTIGATOR	SCREEN	10	SCREEN	2010-01-02	-2	
2 (cont)	SCINTIGRAPHY	INVESTIGATOR	SCREEN	10	SCREEN	2010-01-01	-3	
3 (cont)	CT SCAN	INVESTIGATOR	SCREEN	10	SCREEN	2010-01-02	-2	EFFUSION

TU NSV Metadata

Variable	Label	Type	Role	Origin
PRTYP	Tumor or Lesion Presentation Type	text	Non-Standard Record Qualifier	CRF

The tumors were identified by CT SCAN of the CHEST/ABDOMEN/PELVIS and SCINTIGRAPHY of the BONE, which is recorded in PR. Further imaging was performed at each subsequent disease assessment time point. PRREFID holds the image identifier.

Rows 1-2: Show the imaging performed at screening that identified the tumors listed in TU above.
Row 3: Shows the CT scan of the subject's torso (described in PRLOC as MULTIPLE and PRLOC1/PRLOC2/PRLOC3 as ABDOMEN/CHEST/PELVIS) performed at Week 12.
Row 4: Shows that the bone scintigraphy was not performed at Week 12.
Rows 5-6: Shows the imaging performed at Week 24.

pr.xpt

Row	STUDYID	DOMAIN	USUBJID	PRSEQ	PRREFID	PRLNKGRP	PRTRT	PRPRESP	PROCCUR	PRLOC	EPOCH
1	VWX7777	PR	VWX7777-90000	1	IMG-00001	A1	CT SCAN	Y	Y	MULTIPLE	SCREEN
2	VWX7777	PR	VWX7777-90000	2	IMG-00002	A1	SCINTIGRAPHY	Y	Y	BONE	SCREEN
3	VWX7777	PR	VWX7777-90000	3	IMG-00003	A2	CT SCAN	Y	Y	MULTIPLE	TREATMENT
4	VWX7777	PR	VWX7777-90000	4	IMG-00004	A2	SCINTIGRAPHY	Y	N	BONE	TREATMENT
5	VWX7777	PR	VWX7777-90000	5	IMG-00005	A3	CT SCAN	Y	Y	MULTIPLE	TREATMENT
6	VWX7777	PR	VWX7777-90000	6	IMG-00006	A3	SCINTIGRAPHY	Y	Y	BONE	TREATMENT

Row	VISITNUM	VISIT	PRSTDTC	PRSTDY	PRLOC1	PRLOC2	PRLOC3
1 (cont)	10	SCREEN	2010-01-02	-2	ABDOMEN	CHEST	PELVIS
2 (cont)	10	SCREEN	2010-01-01	-3			
3 (cont)	20	WEEK 12	2010-03-29	85	ABDOMEN	CHEST	PELVIS
4 (cont)	20	WEEK 12					
5 (cont)	30	WEEK 24	2010-06-23	171	ABDOMEN	CHEST	PELVIS
6 (cont)	30	WEEK 24	2010-06-24	172			

PR NSV Metadata

Variable	Label	Type	Codelist	Role	Origin
PRLOC1	Procedure Location 1	text	Anatomical Location	Non-Standard Record Qualifier	CRF
PRLOC2	Procedure Location 2	text	Anatomical Location	Non-Standard Record Qualifier	CRF
PRLOC3	Procedure Location 3	text	Anatomical Location	Non-Standard Record Qualifier	CRF

The TR domain would hold records for measurements and/or assessments of the target and non-target tumors/sites of disease during the study (refer to SDTM Examples for Oncology Use Cases (available at: http://wiki.cdisc.org/x/5yuyAQ) Example 14).

The RS domain holds records for the target and non-target tumors/sites of disease response to treatment, as defined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Rows 1-3: The tumors show partial response (PR) to treatment in Week 12. Note that the non-target response (Row 2) is given as "Not All Evaluated" due to the lack of a bone scintigraphy image (pr.xpt, Row 4). TR would hold a record that states the scan was not performed for at least one non-target lesion. The sample data and modeling are from SDTM Examples for Oncology Use Cases (available at: http://wiki.cdisc.org/x/5yuyAQ), Example 14.
Rows 4-6: The tumors show complete response (CR) to treatment in Week 24, indicating that all signs of cancer have disappeared.

rs.xpt

Row	STUDYID	DOMAIN	USUBJID	RSSEQ	RSLNKGRP	RSTESTCD	RSTEST	RSCAT	RSORRES	RSSTRESC	RSEVAL	EPOCH
1	VWX7777	RS	VWX7777-90000	1		TRGRESP	Target Response	RECIST 1.1	PR	PR	INVESTIGATOR	TREATMENT
2	VWX7777	RS	VWX7777-90000	2		NTRGRESP	Non-Target Response	RECIST 1.1	NOT ALL EVALUATED	NOT ALL EVALUATED	INVESTIGATOR	TREATMENT
3	VWX7777	RS	VWX7777-90000	3	A2	OVRLRESP	Overall Response	RECIST 1.1	PR	PR	INVESTIGATOR	TREATMENT
4	VWX7777	RS	VWX7777-90000	4		TRGRESP	Target Response	RECIST 1.1	CR	CR	INVESTIGATOR	TREATMENT
5	VWX7777	RS	VWX7777-90000	5		NTRGRESP	Non-Target Response	RECIST 1.1	CR	CR	INVESTIGATOR	TREATMENT
6	VWX7777	RS	VWX7777-90000	6	A3	OVRLRESP	Overall Response	RECIST 1.1	CR	CR	INVESTIGATOR	TREATMENT

Row	VISITNUM	VISIT	RSDTC	RSDY
1 (cont)	20	WEEK 12	2010-03-29	85
2 (cont)	20	WEEK 12	2010-03-29	85
3 (cont)	20	WEEK 12	2010-03-29	85
4 (cont)	30	WEEK 24	2010-06-23	171
5 (cont)	30	WEEK 24	2010-06-23	171
6 (cont)	30	WEEK 24	2010-06-23	171

Relationships between datasets are defined in RELREC. An ellipsis has been substituted for the relationships involving the TR domain because it was not shown in this example.

relrec.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
…	…	…	…	…	…	…	…
5	VWX7777	TU		TUREFID		MANY	A
6	VWX7777	PR		PRREFID		ONE	A
7	VWX7777	PR		PRLNKGRP		MANY	D
8	VWX7777	RS		RSLNKGRP		ONE	D

For additional dataset examples related to disease response, see Section 4.3.1, SDTM Examples for Oncology Use Cases (available at: http://wiki.cdisc.org/x/5yuyAQ), and/or SDTMIG v3.2 Section 6.3 - TU, TR, and RS Domains.

4.3 Disease Recurrence

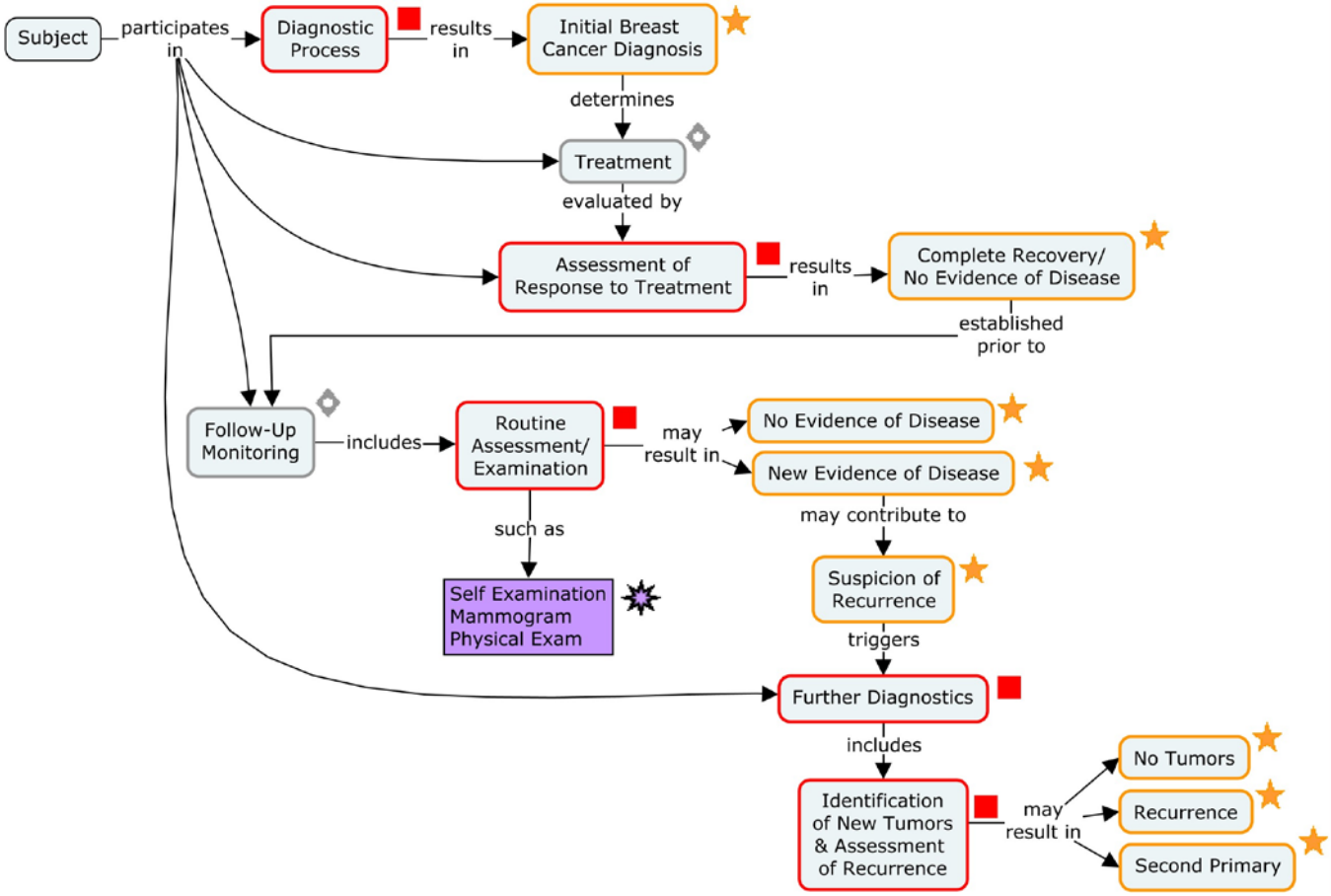
Occasionally, breast cancer can return after primary treatment. Suspicion of recurrence may result from self-assessment, routine mammogram, or physician assessment. If there is a suspicion of breast cancer recurrence, imaging and/or biopsy will take place to confirm or rule out recurrence.

Recurrent breast cancer is often classified by the location of the recurrence relative to the original site:

- **Local Recurrence:** Cancerous tumor cells remain in the original site and, over time, grow back. Many physicians do not consider local breast cancer recurrence to be the spread of breast cancer, but rather, failure of the primary treatment. Even after mastectomy, portions of the breast skin and fat remain, and local recurrence is possible.

- **Regional Recurrence:** A regional recurrence of breast cancer is more serious than local recurrence because it usually indicates that the cancer has spread past the breast and the axillary lymph nodes. Regional breast cancer recurrences can occur in the pectoral muscles, in the internal mammary lymph nodes under the breastbone and between the ribs, in the supraclavicular nodes, and in the nodes surrounding the neck.
- **Distant Recurrence:** A distant breast cancer recurrence, also known as a metastasis, is the most dangerous type of recurrence. Once out of the breast, cancer usually spreads first to the axillary lymph nodes. Breast cancer may spread to other sites including the bone marrow, lungs, liver, brain, or other organs.

Both the previous breast cancer treatment and breast cancer recurrence type will be considered in determination of the treatment.



Concept Map 5: Recurrence of Breast Cancer

4.3.1 Examples for Disease Recurrence

Example 1

Disease response assessments related to disease recurrence in the adjuvant and neoadjuvant setting are provided below. Examples of response assessment to palliative therapy are provided in Section 4.2.1. This example shows two radiological assessments: Disease recurrence was not identified at the first assessment, but was identified at the second assessment. The sample data and modeling are from SDTM Examples for Oncology Use Cases (available at: http://wiki.cdisc.org/x/5yuyAQ), Example 12.

In this example, the subject was monitored for signs of recurrence, with CT scanning of the chest and abdomen/pelvis and an MRI of the head performed at each disease assessment time point. These scans were performed per protocol to look for recurrence. Unfortunately for this subject, disease recurrence was identified in various locations at Week 36. A local disease recurrence was identified in the left breast; regional disease recurrence was identified in the internal mammary and infraclavicular lymph nodes on the same side; and distant disease recurrence was identified in the liver and colon.

The PR domain holds the records of the scanning procedures performed. The image identifier for each resulting scan is in PRREFID.

Rows 1-3: Show the CT scanning and MRI performed at screening. There are no TU records associated with these scans, which is in keeping with an adjuvant setting.
Rows 4-6: Show the CT scanning and MRI performed at Week 20. There are no TU records associated with these scans either.
Rows 7-8: Show the CT scanning performed at Week 36. Note that the values in PRREFID (IMG-00007 and IMG-00008) match those in TUREFID for Rows 1-6 of the tu.xpt example below.
Row 9: Shows the MRI performed of the head at Week 36, which did not identify any disease recurrence.

pr.xpt

Row	STUDYID	DOMAIN	USUBJID	PRSEQ	PRREFID	PRLNKGRP	PRTRT	PRPRESP	PROCCUR	PRLOC	EPOCH	VISITNUM	VISIT
1	PQR4444	PR	PQR4444-70000	1	IMG-00001	A1	CT SCAN	Y	Y	CHEST	SCREEN	10	SCREEN
2	PQR4444	PR	PQR4444-70000	2	IMG-00002	A1	CT SCAN	Y	Y	ABDOMEN/PELVIS	SCREEN	10	SCREEN
3	PQR4444	PR	PQR4444-70000	3	IMG-00003	A1	MRI	Y	Y	HEAD	SCREEN	10	SCREEN
4	PQR4444	PR	PQR4444-70000	5	IMG-00004	A2	CT SCAN	Y	Y	CHEST	TREATMENT	80	WEEK 20
5	PQR4444	PR	PQR4444-70000	6	IMG-00005	A2	CT SCAN	Y	Y	ABDOMEN/PELVIS	TREATMENT	80	WEEK 20
6	PQR4444	PR	PQR4444-70000	7	IMG-00006	A2	MRI	Y	Y	HEAD	TREATMENT	80	WEEK 20
7	PQR4444	PR	PQR4444-70000	8	IMG-00007	A3	CT SCAN	Y	Y	CHEST	TREATMENT	120	WEEK 36
8	PQR4444	PR	PQR4444-70000	9	IMG-00008	A3	CT SCAN	Y	Y	ABDOMEN/PELVIS	TREATMENT	120	WEEK 36
9	PQR4444	PR	PQR4444-70000	10	IMG-00009	A3	MRI	Y	Y	HEAD	TREATMENT	120	WEEK 36

Row	PRSTDTC	PRSTDY
1 (cont)	2010-01-01	-3
2 (cont)	2010-01-01	-3
3 (cont)	2010-01-01	-3
4 (cont)	2010-05-27	144
5 (cont)	2010-05-28	145
6 (cont)	2010-05-28	145
7 (cont)	2010-09-17	257
8 (cont)	2010-09-17	257

Row	PRSTDTC	PRSTDY
9 (cont)	2010-09-17	257

Rows 1-3: Show the disease recurrence identified by the Week 36 CT scan of the chest (TUREFID = IMG-00007).
Rows 4-5: Show the disease recurrence identified by the Week 36 CT scan of the abdomen and pelvis (TUREFID = IMG-00008).

tu.xpt

Row	STUDYID	DOMAIN	USUBJID	TUSEQ	TUREFID	TULNKID	TUTESTCD	TUTEST	TUORRES	TUSTRESC
1	PQR4444	TU	PQR4444-70000	1	IMG-00007	LOC01	DRCRLTLC	Disease Recurrence Relative Location	LOCAL	LOCAL
2	PQR4444	TU	PQR4444-70000	2	IMG-00007	REG01	DRCRLTLC	Disease Recurrence Relative Location	REGIONAL	REGIONAL
3	PQR4444	TU	PQR4444-70000	3	IMG-00007	REG02	DRCRLTLC	Disease Recurrence Relative Location	REGIONAL	REGIONAL
4	PQR4444	TU	PQR4444-70000	4	IMG-00008	DIS01	DRCRLTLC	Disease Recurrence Relative Location	DISTANT	DISTANT
5	PQR4444	TU	PQR4444-70000	5	IMG-00008	DIS02	DRCRLTLC	Disease Recurrence Relative Location	DISTANT	DISTANT

Row	TULOC	TULAT	TUMETHOD	TUEVAL	EPOCH	VISITNUM	VISIT	TUDTC	TUDY
1 (cont)	BREAST	LEFT	CT SCAN	INVESTIGATOR	TREATMENT	120	WEEK 36	2010-09-17	257
2 (cont)	INTERNAL MAMMARY LYMPH NODE		CT SCAN	INVESTIGATOR	TREATMENT	120	WEEK 36	2010-09-17	257
3 (cont)	INFRACLAVICULAR LYMPH NODE		CT SCAN	INVESTIGATOR	TREATMENT	120	WEEK 36	2010-09-17	257
4 (cont)	LIVER		CT SCAN	INVESTIGATOR	TREATMENT	120	WEEK 36	2010-09-17	257
5 (cont)	COLON		CT SCAN	INVESTIGATOR	TREATMENT	120	WEEK 36	2010-09-17	257

The TR domain would hold a record for each identified location of recurrence. The test Tumor State (TUMSTATE) could be used with the value of PRESENT (refer to SDTM Examples for Oncology Use Cases (available at: http://wiki.cdisc.org/x/5yuyAQ) Example 12).

The RS domain holds the disease's response to treatment. In this example, the test is a simple query: "Has disease recurrence been identified?" which is given as an indicator, like so:

Row 1: Disease recurrence was not identified at Week 20.
Row 2: Disease recurrence was identified at Week 36.

rs.xpt

Row	STUDYID	DOMAIN	USUBJID	RSSEQ	RSGRPID	RSLNKGRP	RSTESTCD	RSTEST	RSCAT
1	PQR4444	RS	PQR4444-70000	1		A2	DRCRIND	Disease Recurrence Indicator	PROTOCOL DEFINED RESPONSE CRITERIA
2	PQR4444	RS	PQR4444-70000	2		A3	DRCRIND	Disease Recurrence Indicator	PROTOCOL DEFINED RESPONSE CRITERIA

Row	RSORRES	RSSTRESC	RSEVAL	EPOCH	VISITNUM	VISIT	RSDTC	RSDY
1 (cont)	N	N	INVESTIGATOR	TREATMENT	80	WEEK 20	2010-05-27	144
2 (cont)	Y	Y	INVESTIGATOR	TREATMENT	120	WEEK 36	2010-09-17	257

Relationships between datasets are defined in RELREC. An ellipsis has been substituted for the relationships involving the TR domain because it was not shown in this example.

relrec.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
1	PQR4444	PR		PRREFID		ONE	A
2	PQR4444	TU		TUREFID		MANY	A
…	…	…	…	…	…	…	…
7	PQR4444	PR		PRLNKGRP		MANY	D
8	PQR4444	RS		RSLNKGRP		ONE	D

Example 2

This example is for a trial in a neoadjuvant setting where the primary objective is to compare the rate of pathologic complete response (pCR) in the breast at time of surgery in the study treatment arms. In this example, the study treatment was given for eight weeks prior to surgery. This example has been adapted from SDTM Examples for Oncology Use Cases (available at: http://wiki.cdisc.org/x/5yuyAQ), Example 15.

Data not shown in this example include:

- The CT scan (PR) that identified the tumor (TU)
- The preliminary biopsy (PR) to confirm pathologically that the tumor was cancerous (MI), and to plant a tracer chip for later surgery (DI, DO, DT (see SDTMIG-MD for guidance on handling data pertaining to medical devices))
- Eight weeks of neoadjuvant treatment (EX/EC)
- The breast resection and sentinel node biopsy at the end of Week 8 (PR) and associated pathologic examinations (MI) that confirmed pCR according to the protocol

The pCR itself, as a response of the disease to treatment, is shown in the RS example below.

rs.xpt

Row	STUDYID	DOMAIN	USUBJID	RSSEQ	RSTESTCD	RSTEST	RSCAT	RSORRES	RSSTRESC	RSEVAL	EPOCH	VISITNUM
1	IHR0298	RS	IHR0298-11100	1	PATHRESP	Pathologic Response	WHO BREAST	pCR	pCR	INVESTIGATOR	TREATMENT	40

Row	VISIT	RSDTC	RSDY
1 (cont)	WEEK 8	20010-04-02	74

5 Analysis Data

This section illustrates the use of the Analysis Data Model (ADaM) to create datasets to support the analysis of endpoints common to breast cancer trials. Adherence to the basic principles of ADaM ensures that the analysis datasets support traceability back to the source SDTM data. This traceability provides the consumer of the analysis dataset with the understanding of how derived data were developed and how the data can be used to generate the statistical results.

This section is not intended to illustrate every possible variable that might be included in analysis datasets created for statistical analysis of BrCa. Additionally, the examples are intended to be descriptive and illustrative of the use of the ADaM model, and should not be interpreted as the complete analysis requirements for BrCa trials. The metadata and derivations presented are for illustrative purposes only, and are not meant to imply a universally accepted definition or derivation of the variables. The examples should not be viewed as a statement of the standard themselves but rather an example of the application of the ADaM

standard to the development of analysis ready datasets. Please refer to Version 2.1 of the Analysis Data Model and Version 1.1 of the Analysis Data Model Implementation Guide (ADaMIG) for required background about the ADaM and the ADaM data structures.

This section focuses on just a few of the most common analysis endpoints used in breast cancer trials. There are additional analysis endpoints that are not illustrated and will be considered for inclusion in future TAUGs.

It is noted that the analysis of oncology data is complex. In addition to the ADaM examples, this TAUG strives to describe the most common definitions for the derivation of analysis endpoints and any associated analysis issue, but there will always be exceptions to these recommendations. Readers must take responsibility to determine whether the statements and examples presented below are appropriate for their given trial and, if not, adapt their implementation accordingly.

5.1 Analysis Endpoints

Analysis endpoints can be split into two categories of time-to-event (TTE) and response endpoints. TTE endpoints include outcomes such as date of death or date of progression. Response endpoints are typically based on standardized definitions of response (e.g. RECIST), and are typically dichotomized between levels of clinically relevant response (PR/CR) versus not clinically relevant (SD/PD), though other splits and analyses are possible.

The derivation of TTE endpoints is based on dates that define the start of the observation period and dates that define the occurrence of the event or the end of the observation period, in the case of censoring. In oncology trials, the date of the start of the observation period is generally easy to identify, but the date associated with the event or censoring may require a detailed comparison between multiple candidate dates. The analysis issues associated with censoring are common to all time-to-event endpoints. Therefore, in the discussion below, issues associated with censoring are discussed within Section 5.1.1.1 and not repeated for subsequent sections.

5.1.1 Time to Event

5.1.1.1 Progression-free Survival – (PFS)

The usual definition of PFS is the length of time until progression or death from any cause. For patients without a PFS event, PFS is censored at the last adequate assessment (see Section 5.1.1.1.1, under Missing Assessments), as described in the analysis plan, indicating non-progression.

A PFS event in breast cancer is usually identified by a progressive disease (PD) response in RECIST or by an occurrence of death if it occurs prior to documented progression.

PFS for patients without progression or death will be the time until the last time the patient was known to be progression-free as per protocol specified criteria. These patients without a PFS event are deemed to have a censored PFS value with the presence of censoring indicated by an accompanying censoring variable which is categorical in nature (e.g., 0=Had the event, ≥1= Did not have the event (censored)). Any time-to-event analysis of PFS will require both the derivation of PFS and the censoring variable.

The study protocol should specify that response data used for the PFS endpoint are captured according to an assessment schedule which might vary over the course of the study (e.g., quarterly in the first two years, and then after every 6 months). In addition to the overall response assignment (CR/PR/SD/PD/UNK),

the individual tumor data and/or intermediate components of overall response (e.g., non-target lesion response, new lesions) may be collected at these assessment visits.

Determination of progression may be made by the investigator at the local site, an independent central review process, or derived from the raw tumor data (from local site and/or central review) via a programming algorithm. Usually one of these is regarded as the primary data source for analysis, with one or more of the alternative data sources used for sensitivity analyses.

5.1.1.1.1 Derivation Considerations

Start of Observation Period for Analysis
For randomized studies, the usual start date for the PFS calculation is the date of randomization. For non-randomized studies (and, in particular, single-arm studies), the usual start date for the PFS calculation is the start date of therapy. Occasionally (e.g., for registry type studies, or perhaps where one arm does not have an interventional therapy) an alternative start date, such as date of original diagnosis, may be used. For any specific study, PFS is analyzed based on an observation period start date; sensitivity analyses using additional observation period start dates are not normally required.

Date of Event or Censoring
The exact date of progression according to a RECIST response evaluation may not always be straightforward, since scans and evaluations of different regions may be performed on separate days and may even be on a different day to the patient assessment visit. Often a rule is employed to derive the date of progression, such as earliest scan or evaluation date used to derive the overall response evaluation of PD for that visit.

Patients without progression or death are normally censored at the last date of adequate radiologic assessment. An adequate radiologic assessment is normally a visit in which the subject is evaluated for disease progression, and it may occur prior to subject withdrawal from the study. Usually, evidence of non-progression would require a stable disease classification or better.

Typical censoring rules for PFS:

- Subjects who started new anti-cancer therapy prior to documented PD or death will be censored at the last radiological assessment prior to initiation of new anti-cancer therapy;
- Subjects who did not have PD or death will be censored at the last radiological assessment;
- Subjects who had PD or death after missing two or more consecutive scheduled radiological assessments will be censored at the last prior adequate radiological assessment;
- Subjects who had no baseline or post-baseline radiological assessment will be censored on Day 1, unless the subject died within <n> days of Day 1, in which case the subject will be considered as having an event at the date of death.
- When an analysis cutoff date is implemented, only data (deaths and radiological assessments) occurring on or prior to the cutoff date will be used for analysis.

Interventions that influence determination of date of event or censoring
Sometimes before a progressive event occurs, the patient may have an intervention that takes priority over the date of the progressive event. These interventions can include withdrawals from treatment or adverse events requiring treatment that conflicts with the study treatment. The following are examples of situations that may impact censoring rules, although this list is by no means exhaustive.

Interventions dependent on disease state (usually indicating disease worsening)
Sometimes the worsening of disease might not be captured and documented via a PD response according to RECIST, but the investigator might withdraw the patient from treatment and from further follow-up because of clinical signs and symptoms, i.e., clinical progression. The patient could be censored according to the RECIST radiologic PFS definition, but since they were withdrawn from treatment or study due to reasons related to change in disease status prior to radiologic documentation, a routine censoring algorithm may result in biased estimates. This situation is described as informative censoring and therefore sensitivity analyses may be conducted. These sensitivity analyses might include the imputation of best or worst case scenarios or other imputation techniques for missing data.

If another anti-cancer therapy is given during the trial before documented progression indicates a worsening of disease, then the impact on the PFS endpoint derivation and the subsequent analysis should be considered. For example, although the primary analysis still might need to be censored at the last non-PD assessment prior to the alternative therapy, sensitivity analyses might look at alternative derivations (e.g., handling the therapy as an event or ignoring the therapy completely (assuming additional response follow-up beyond the start of this therapy)).

Other Interventions
There may be other factors not necessarily connected to the disease that might impact the PFS endpoint (e.g., during the study an incorrect dose is given to the patient, or there is a problem with the randomization so that the alternative treatment from the other arm is received). In these cases, one could simply ignore these interventions as part of an ITT (Intent to Treat) approach, or alternative approaches might be considered (e.g., censoring at the last response assessment prior to intervention as part of a per-protocol evaluation).

Missing or Unscheduled Assessments

Missing Assessments
The absence of data used to determine a missing response can either arise because the assessment visit itself has been missed or delayed, or because of an UNK response was recorded at the assessment (which would effectively be ignored in the analysis). For PFS, only assessments missing after the last non-PD assessment are of direct concern, and in particular when the missing assessment leads to a large gap between the last non-PD assessment and an observed PFS event. It could be argued that the event might have been observed earlier had assessments not been missing.

When a relatively large percentage of patients in a study have missing assessments prior to events, this can lead to concerns that the PFS estimates are inflated. If the degree of missing assessments is imbalanced between treatment groups, the analysis of treatment effects can be biased.

Therefore, rather than ignore this issue, various rules can be employed to cope with missing assessments. For example, patients with two or more missing visits prior to a PFS event may be censored at the last adequate assessment prior to the missing visit. Alternatively, for a type of “worst case” analysis, a PFS event could be assigned at the next protocol-scheduled assessment after the last non-PD evaluation.

Unscheduled Assessments
Another possible source of bias can occur when there are unscheduled assessments prior to a protocol-scheduled visit. For example, this may occur if a subject has worsening of clinical symptoms that are related to the disease and scans are taken earlier to check for possible progression.

Although the data arising from this kind of scenario can be handled by the type of statistical method chosen (such as interval censoring), another way is to address this problem within the PFS endpoint derivation by assigning any PDs found at early unscheduled visits to the next scheduled assessment. Within the

same analysis, it is also possible to handle PDs found following missed or delayed assessment visits by backdating the PD to an earlier protocol-scheduled assessment visit date. These modifications to the endpoint derivation are usually performed for sensitivity analyses to support the primary PFS analysis.

5.1.1.1.2 Modifications of Endpoint Derivation for Sensitivity Analyses

The derivation of PFS can involve a number of decisions regarding issues such as data source (central review, local site, recalculated), event definition (include/exclude clinical progressions), derivation of event date, presence of missing assessments, etc. The usual approach is to decide upfront on the most appropriate options for the single primary analysis. However, to show the robustness of the primary analysis to some of the key assumptions, one or more sensitivity analyses are sometimes employed. When multiple approaches for defining PFS are used within one study, the supporting ADaM dataset would use separate PARAM and PARAMCD values to uniquely identify each of these parameter derivations.

5.1.1.2 Overall Survival – (OS)

Overall survival is defined as the time from the date of randomization (randomized trials) or the date of first dose (non-randomized trials) until the date of death from any cause. Subjects who are alive or lost to follow-up at the analysis are censored at the last known alive date. When an analysis cutoff date is implemented, only deaths occurring on or prior to the cutoff date are counted as OS events. Subjects with death or last known alive date after the analysis cutoff date will be censored at the analysis cutoff date.

The same considerations for OS in breast cancer apply as in virtually all other oncology indications. The death event can be considered a hard endpoint, in that it is unusual for the timing of the death to be in question. Similarly, for patients without a death, the “alive” status is usually not in question, but it will rely on collection of the appropriate data to properly document the last time the patient was known to be alive (e.g., the last contact date).
As with other time-to-event endpoints, the OS time variable also requires a censoring variable in order to analyze the endpoint using time-to-event methods.

5.1.1.2.1 Derivation Considerations

Start of Observation Period for Analysis
For randomized studies, the usual start date for the OS calculation is the date of randomization. For non-randomized studies (and in particular, single-arm studies), the start date of therapy is usually employed for the derivation. Occasionally (e.g., for registry type studies, or perhaps where one arm does not have an interventional therapy), an alternative start date, such as date of original diagnosis and/or date of qualification for including subject into the study, may be used. For any specific study, OS is analyzed based on a particular observation period start date and sensitivity analyses using additional observation period start dates are not normally required.

Date of Death or Last Contact Date
The date of death is recorded on the case report forms and can usually be relied upon to be correct. For patients who did not die, the last known alive date needs to be derived from the existing data collected in the study. This can come either from a specific survival follow-up form in the survival follow-up phase or from other data that indicate the last date when the patient was known to be alive.

The fact that a patient is alive while on treatment is often not collected specifically, but is inferred from the other data collected. However, for patients dying during this main study period, the death information is collected. Following withdrawal of therapy and/or other follow-up assessments, the survival status and any death information for each patient may be collected in a survival follow-up period.

Interventions
In comparison to the PFS endpoint, for OS there is often less need to take account of specific interventions occurring while a patient is still alive. The ITT principle is often adhered to quite closely, since it is anticipated that once the patient is off study, various factors will affect the risk of death, including additional alternative anti-cancer therapies. Nevertheless, there sometimes may be a need to perform sensitivity analyses to evaluate the robustness of the main analysis (e.g., if a number of patients switched to the therapy in the alternative treatment arm as a major deviation from protocol, one type of sensitivity analysis might be to censor the OS endpoint at time of crossover).

Missing Visits
Incomplete survival follow-up due to missed visits can be an issue for the OS analysis, especially if this differs between treatment groups. For example, if investigators do not diligently follow up with the patients on one treatment, this can lead to biased survival estimates and analysis results.

5.1.1.2.2 Modifications of Endpoint Derivation for Sensitivity Analyses

The complexity of the OS endpoint derivation is much reduced in terms of the number of factors to consider, compared with the PFS endpoint. Because of this, and the fact that there is often greater focus on an ITT approach for this endpoint, the need for sensitivity analyses involving changes to OS duration or censoring variable is much reduced, although some may be considered.

5.1.1.2.3 Other Relevant Supportive Analyses

A summary giving the reasons for censoring can be a useful supplement to the main OS analyses. If there are a large number censored due to loss to follow-up, particularly in one group compared to the other, then care is needed in the interpretation of the endpoint and further analysis is suggested.

5.1.1.3 Event-free Survival – (EFS)

In a neoadjuvant setting, the purpose of event-free survival is to describe what happens to the disease while the subject is being treated. The calculation of EFS is defined as the length of time from a start date until either death or until progression of the disease occurs that precludes surgery, including both local and distant recurrence.

The method for determining event-free survival is similar to that for determining progression-free survival in Section 5.1.1.1 above. The same rules for determining the start date apply. For determining the date of the event, the date of death and either the local or distant recurrence of the disease are the same as PFS, the one difference being that progression of disease prior to surgery should be included in EFS.

5.1.1.4 Disease-free Survival – (DFS)

In an adjuvant setting, the purpose of disease-free survival is to assess survival in the context of disease recurrence following removal of the primary tumor and affected lymph nodes. This can also be referred to as relapse-free survival or RFS. The calculation of DFS is the length of time from a start date until the patient survives without any evidence of disease recurrence or death.

The method for determining disease-free survival is similar to that for determining progression-free survival in Section 5.1.1.1 above. The same rules for determining the start date apply. For determining the date of the event, either the date of death or the date on which any disease recurrence is detected is used. No interventions should be used to in determining DFS.

5.1.1.5 Duration of Response – (DOR)

The duration of overall response (DOR) is measured from the time that RECIST criteria are met for complete response (CR) or partial response (PR), depending on the definition within the specific analysis plan, until the first date that recurrent or progressive disease is objectively documented. It is limited to subjects who have achieved either PR or CR during the course of treatment.

In evaluating duration of response, there are also some variations that are used. These include duration of overall complete response, which only analyzes subjects who achieved complete response, and duration of stable disease, which analyzes when a subject achieves either complete response, partial response, or stable disease. In both cases, the timing ends at the point a subject's disease progresses.

5.1.1.5.1 Derivation Considerations

Start of Observation Period for Analysis
The observation period start date for duration of response is calculated for each subject as the date on which that subject achieves either complete response (CR) or partial response (PR) after the start of the study. If subjects do not achieve either CR or PR, then they will not be included in the duration of response calculation. The date for the start of CR and PR may also differ from the date of best overall response if a subject achieves a partial response reading followed by a complete response.

5.1.2 Response Endpoints

5.1.2.1 Best Overall Response – (BOR)

Best overall response (BOR) is defined as the best response recorded from the start of the trial, normally the date of randomization, until disease progression occurs, evidenced by either RECIST assessment or death, or the patient discontinues treatment.

When performing this analysis, the ranking for best response is considered to be complete response (CR), partial response (PR), stable disease (SD)/(Non Complete Response/Non Progressive Disease (NON-CR/NON-PD) for non-measurable disease), and progressive disease (PD), in that order. Best overall response can be calculated either for the entire time a subject was on the trial or for a specific period of time, such as a combination therapy followed by maintenance therapy.

Unlike the survival analysis, the BOR analysis is based only on assessments until progressive disease is assessed. For that reason, considerations for missing visits are not generally taken into account. For assessment, the BOR is analyzed by populations achieving each of the RECIST categories during the clinical trial period.

5.2 Table Shells

The analysis datasets shown below are designed to support the analyses summarized in these two target table shells. These shells are intended to be used as examples only and do not establish an expectation for the types of tables to be used in a clinical trial

Table 5.2.1: Categorical Analysis of Tumor Response

ANALYSIS OF RADIOGRAPHIC TUMOR RESPONSE BY THE CENTRAL IMAGING CENTER
EFFICACY POPULATION

VARIABLE	*Treatment A* ***(N=XX)***	*Treatment B* ***(N=XX)***	***P-VALUE***
BEST RESPONSE			
COMPLETE RESPONSE (CR)	XX/XX (XX.X)	XX/XX (XX.X)	0.XXXX
PARTIAL RESPONSE (PR)	XX/XX (XX.X)	XX/XX (XX.X)	0.XXXX
STABLE DISEASE (SD)	XX/XX (XX.X)	XX/XX (XX.X)	0.XXXX
DISEASE PROGRESSION (PD)	XX.XX (XX.X)	XX/XX (XX.X)	0.XXXX
UNKNOWN (UNK)	XX.XX (XX.X)	XX/XX (XX.X)	0.XXXX
OVERALL RESPONSE (CR+PR)	XX/XX (XX.X)	XX/XX (XX/X)	
95% CI&	XX.X – XX.X	XX.X – XX.X	0.XXXX

@INCLUDES SUBJECTS WITH AT LEAST ONE MEASURABLE LESION AT BASELINE.
&95% CONFIDENCE INTERVAL OF OBJECTIVE RESPONSE RATE IS FROM THE EXACT BINOMIAL DISTRIBUTION.

Table 5.2.2: Analysis of Time to Progression

ANALYSIS OF RADIOLOGICAL PROGRESSION
EFFICACY POPULATION

VARIABLE	TREATMENT A ***(N=XX)***	TREATMENT B ***(N=XX)***	TOTAL ***(N=XX)***
PERCENTILES			
25TH (95% CI)	XXX (XX.X, XX.X)	XXX (XX.X, XX.X)	XXX (XXX.XX)
50TH (95% CI)	XXX (XX.X, XX.X)	XXX (XX.X, XX.X)	XXX (XXX.XX)
75TH (95% CI)	XXX (XX.X, XX.X)	XXX (XX.X, XX.X)	XXX (XXX.XX)
HAZARD RATIO			0.XXXX
P-VALUE			0.XXXX
ESTIMATES AT TIMEPOINT			
1ST TIMEPOINT	XXX (XX.X, XX.X)	XXX (XX.X, XX.X)	XXX (XXX.XX)
2ND TIMEPOINT	XXX (XX.X, XX.X)	XXX (XX.X, XX.X)	XXX (XXX.XX)
3RD TIMEPOINT	XXX (XX.X, XX.X)	XXX (XX.X, XX.X)	XXX (XXX.XX)
SUBJECTS WITH EVENTS	XXX	XXX	
SUBJECTS CENSORED	XXX	XXX	
REASONS FOR CENSORING			
WITHDRAW TO AE	XXX	XXX	
PROTOCOL VIOLATION	XXX	XXX	

5.3 Analysis Datasets

The following sections illustrates the use of the ADaM model to create datasets designed to support analyses of the analysis endpoints discussed above. In practice, the first step toward developing the content of an analysis dataset is to review the types of analyses specified in the statistical analysis plan and presented in mock table shells. The two examples of table shells shown above provide the target for the type of analyses the datasets need to support. Because of space limitations, only key variables are shown below but typically many other variables as described in the ADaM IG would be present in an analysis dataset that follow the ADaM principles.

An abbreviated subject-level analysis dataset (ADSL) is shown that contains sponsor-defined variables that would be of typical importance to many breast cancer trials. A series of ADaM datasets, including an intermediate dataset, is then presented. The purpose of the intermediate dataset is to collate all of the data that are important for the derivation of primary endpoints. This intermediate dataset is used as input for the development of the analysis dataset that supports the creation of the statistical analyses. The primary reason for the creation of an intermediate dataset is to support traceability. An alternate approach that uses standalone datasets, which contain more variables and robust metadata, could equally support traceability. As is the case for any ADaM implementation, it is left up to the producer to decide the best process that will fulfill the principles of clear communication and traceability.

This section is not intended to illustrate every possible variable that might be included in analysis datasets created for statistical analysis of breast cancer endpoints. Additionally, the examples are intended to be descriptive and illustrative of the use of the ADaM model and should not be interpreted as the complete analysis requirements for cancer trials. The metadata and derivations presented are for illustrative purposes only and are not meant to imply a universally accepted definition or derivation of the variables. The examples should not be viewed as a statement of the standard themselves, but rather as an example of the application of the ADaM standard to the development of analysis-ready datasets

5.3.1 Subject-Level

The Subject-Level Analysis Dataset (ADSL) should be created following the examples described in the ADaM Implementation Guide. The ADaM IG provides a complete description of required and permissible variables that would appear in ADSL, such as population flags, treatment variables, and other important subject level disposition variables. The table below provides discussion on variables that would be of importance for inclusion in a typical ADSL created for BrCa trials.

ADSL Variable Metadata – One record per subject

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Notes
STAGE	Stage of Cancer	Char		This is the stage of cancer that the patient was assessed with at the point of inclusion in the study. Stage is normally captured in an SDTM domain. Guidance on the specific domain will be given in a future version of the TAUG. The codelist can be custom codelist that reflects what is in the SDTM domain. It can have as its controlled terminology ‘STAGE 1,’ ‘STAGE 2,’ ‘STAGE 3,’ ‘STAGE 4,’ or it can use the TNM classification (‘T,’ ‘N,’ ‘M’) or a combination of the two.
HISTOLGY	Histopathology	Char		Histology of the tumor is normally captured in the MI domain.
TRTPREDT	Prior Treatment End Date	Num		If a patient has had prior cancer treatment, the date that the last treatment ended is captured. For example, latest CM.CMENDTC where CM.CMCAT = ‘ANTINEOPLASTIC THERAPY’ or latest PR.PRENDTC where PR.PRCAT = ‘RADIATION THERAPY’ where –DTC variables are converted to numeric date format.

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Notes
HER2STAT	HER2 Status	Char	1+; 2+; 3+; Positive; Negative	This is the HER2 assessment of the subject at randomization. HER2STAT is equal to MI.MISTRESC when MI.MITEST represents HER2 Status. MI.MITEST is subject to sponsor controlled terminology.
ERSTAT	Estrogen Receptor Status	Char	1+; 2+; 3+; Positive; Negative	This is the ER assessment of the subject at randomization. ERSTAT is equal to MI.MISTRESC when MI.MITEST represents Estrogen Receptor Status. MI.MITEST is subject to sponsor-controlled terminology.
VISCERAL	Visceral Disease	Char	Y;N	This is an indicator of whether visceral disease is present. Visceral disease is normally captured in an SDTM domain. Guidance on the specific domain will be given in a future version of the TAUG.

adsl.xpt

Row	STUDYID	USUBJID	SAFFL	EFFFL	TRT01P	TRT01A	TR01SDT	TR01EDT	STAGE	HISTOLGY	TRTPREDT	HER2STAT	ERSTAT	VISCERAL
1	ABC-123	ABC-123-001	Y	Y	TREAT A	TREAT A	2014JAN01	2014AUG15	STAGE 3	DUCTAL	2012FEB14	POSITIVE	Negative	N
2	ABC-123	ABC-123-002	Y	Y	TREAT B	TREAT B	2013NOV13	2013DEC31	STAGE 3	DUCTAL	2011NOV	POSITIVE	1+	N
3	ABC-123	ABC-123-003	Y	Y	TREAT A	TREAT A	2014FEB10	2014NOV15	STAGE 4	LOBULAR	2013JUN30	POSITIVE	3+	Y
4	ABC-123	ABC-123-004	Y	N	TREAT A	TREAT A	2014JUN20	2014NOV29	STAGE 3	LOBULAR	2011AUG28	NEGATIVE	3+	N

5.3.2 Intermediate Event Dataset

For the purpose of analyzing the events of the patient, it is important to identify and collect the possible data elements that could serve as input to the derivation of analysis endpoints. These data elements, such as the dates and results of a radiologic image or other interventions, are described in the protocol and/or within the SAP. By creating a database of these data elements for each subject, the review and understanding of the derivation of time-to-event endpoints analysis is supported. For the purposes of this document and the datasets used below, this will be referred to as an event dataset.

In constructing the event dataset, the different types of events that are evaluated for the time-to-event analysis should be documented as an event within the database. At a minimum, the critical events used to identify the duration for a time-to-event analysis should be included. However, for various reasons such as sensitivity analysis, the choice of dates used to calculate the time to an event can vary depending on the methodology. For example, an assessment of progression might be made by both an investigator and an adjudication committee. These independent assessments may result in the identification of different dates for the qualifying event. This yields a different calculation for the time-to-event analysis. This type of sensitivity analysis is not uncommon in trials where the characterization of important events is not based on a single and universally agreed-upon assessment. This situation is illustrated below by the inclusion of all possible events for a subject that are made using multiple methodologies. Inclusion of all possible methods for determining an event allows for a comparison between these methodologies and an identification of which record was selected over another for the time-to-event analysis. Since traceability is built into the event dataset through the SRCDOM, SRCVAR, SRCSEQ variables, this also gives a reviewer the ability to review all events that were considered for the time-to-event analysis, identify the event that was selected, and consider the impact of the analysis of alternate selections.

Creating the event dataset requires posting records for each event that occurs for each subject. The analysis flag can be used to identify those events that can be used in the time-to-event (TTE) analysis dataset for time-to-event analysis. The basic structure of the event dataset is as follows.

5.3.2.1 Use of a Provisional Variable

Per the ADaM Implementation guide, the content of a parameter (PARAM) should be fully descriptive and not require any additional qualifying variables to fully understand the content of AVAL. Requiring the value of PARAM to fully describe the content of AVAL ensures clarity and communication about the biomedical concept that is being expressed for the value of PARAM. However, there are situations in which the derivation of AVAL for a given parameter concept can vary, not according to the derivation algorithm, but by the methodology used for the calculation. For example, for sensitivity analyses of time-to-event parameters, AVAL may be calculated using different dates depending on choices made by the investigator versus an adjudicator. In this situation, there is no change in the parameter concept and the meaning of AVAL. The CDISC ADaM team is in the early stages of considering whether to allow a special purpose parameter-qualifying variable, PARQUAL. One advantage of using this qualifying variable would be that the same controlled terminology could be used for PARAM and PARAMCD. If ratified, the use of this variable would be limited and would only apply to situations where there is no change in the interpretation of AVAL. The example below utilizes this special purpose variable, but readers should fully appreciate that this variable is provisional and is subject to change.

ADEVENT Variable Metadata – One record per subject per evaluation

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Notes
STUDYID	Study Identifier	Char		ADSL.STUDYID
USUBJID	Unique Subject Identifier	Char		ADSL.USUBJID
TRTP	Planned Treatment	Char		Planned Treatment
ASEQ	Analysis Sequence Number	Num		Sequential number for associating a record number in the ADEVENT dataset. Unique number per subject per parameter per parameter qualifier per analysis start date.
ASTDT	Analysis Start Date	Num		This is the date that the event occurred. RS.RSDTC when PARAMCD = 'ASSESS' DS.DSSTDTC when PARAMCD = 'DISPOSIT' AE.AESTDTC or MH.MHSTDTC or DV.DVSTDTC or CM.CMSTDTC, or PR.PRSTDTC or some other source data for an event which prevents further assessments when PARAMCD = 'EVENT' where –DTC variables are converted to numeric date format.
ASTDY	Analysis Start Relative Day	Num		This is the number of days from randomization to the date of the reported event. ASTDT – ADSL.RANDDT + 1
Proposed *PARQUAL*	*Parameter Qualifier*	*Char*	*INVESTIGATOR; CENTRAL; PATHOLOGIC; PROTOCOL*	*This identifies the source of the Parameter. Investigator for investigator-based assessments; Central for central imaging assessments; Pathologic for an assessment by biopsy; and Protocol for events affecting assessment.*
PARAM	Parameter	Char	ASSESSMENT; DISPOSITION; EVENT	These are the different categories of events that can occur during the execution of the study. ASSESSMENT: The RECIST assessments typically collected from the RS domain. DISPOSITION: These are dispositions collected during the study. Typically expected would be the date randomized, date treatment ended, and date withdrew from study. EVENT: These are events that occur during the conduct of a clinical trial. In some cases, they could be protocol violations or events that prevent further assessments from being made.
PARAMCD	Parameter Code	Char	ASSESS; DISPOSIT; EVENT	Assigned based on the data source. If RECIST assessment then PARAMCD = 'ASSESS' If disposition event then PARAMCD = 'DISPOSIT'

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Notes
				If event that is a protocol violation or prevents further assessments then PARAMCD = 'EVENT'
AVALC	Analysis Value (C)	Char		Reported Assessment associated with the ASTDT.
SRCDESC	Source Event Description	Char		Description of the event of interest. This variable can be populated if there is information in the source for AVALC that can be used in other datasets for censoring information (i.e., a DECOD value for a prohibited medication).
SRCDOM	Source Domain	CHAR		This is the source SDTM domain or ADaM dataset that the record being used for the analysis value can be traced. Set to 'RS' when PARAMCD = 'ASSESS' Set to 'DS' when PARAMCD = 'DISPOSIT' Set to SDTM domain where the event that is a protocol violation or prevents further assessment is represented when PARAMCD = 'EVENT'
SRCVAR	Source Variable	CHAR		This is the variable in the source SDTM domain or ADaM dataset to which the analysis value can be traced. Set to 'AVALC' when PARAMCD = 'ASSESS' Set to 'DSDECOD' when PARAMCD = 'DISPOSIT' Set to SDTM variable where the event that is a protocol violation or prevents further assessment is represented when PARAMCD = 'EVENT'
SRCSEQ	Source Sequence	Num		The sequence number --SEQ or ASEQ of the row in the domain identified in the SRCDOM that relates to the analysis value being derived.
ANL01FL	Analysis Flag 01	Char	Y	Identifies whether the event can be used in time-to-event analysis. This is optional, but can be used if assessments prior to baseline or after a censoring event are included.

adevent.xpt **Proposed**

Row	STUDYID	USUBJID	ASEQ	ASTDT	ASTDY	*PARQUAL*	PARAMCD	AVALC	ANL01FL
1	ABC-123	ABC-123-001	1	2013DEC29	-4	PROTOCOL	DISPOSIT	RANDOMIZED	
2	ABC-123	ABC-123-001	2	2013DEC30	-2	INVESTIGATOR	ASSESS	PD	Y
3	ABC-123	ABC-123-001	3	2013DEC31	-1	CENTRAL	ASSESS	SD	Y
4	ABC-123	ABC-123-001	4	2014JAN01	1	PROTOCOL	DISPOSIT	TREATMENT	Y
5	ABC-123	ABC-123-001	5	2014JAN21	20	INVESTIGATOR	ASSESS	SD	Y
6	ABC-123	ABC-123-001	6	2014JAN22	22	CENTRAL	ASSESS	SD	Y
7	ABC-123	ABC-123-001	7	2014FEB13	44	INVESTIGATOR	ASSESS	PR	Y
8	ABC-123	ABC-123-001	8	2014FEB14	45	CENTRAL	ASSESS	PR	Y
9	ABC-123	ABC-123-001	9	2014MAR06	65	INVESTIGATOR	ASSESS	PR	Y
10	ABC-123	ABC-123-001	10	2014MAR07	66	CENTRAL	ASSESS	PR	Y
11	ABC-123	ABC-123-001	11	2014MAR28	87	INVESTIGATOR	ASSESS	PD	Y
12	ABC-123	ABC-123-001	12	2014MAR29	88	CENTRAL	ASSESS	PD	Y
13	ABC-123	ABC-123-001	13	2014MAR30	89	PROTOCOL	DISPOSIT	TREATMENT	Y
14	ABC-123	ABC-123-001	14	2014MAR31	90	PROTOCOL	EVENT	PROHIB MED	
15	ABC-123	ABC-123-002	1	2013NOV10	-3	PROTOCOL	DISPOSIT	RANDOMIZED	
16	ABC-123	ABC-123-002	2	2013NOV11	-2	INVESTIGATOR	ASSESS	PD	Y
17	ABC-123	ABC-123-002	3	2013NOV12	-1	CENTRAL	ASSESS	PD	Y
18	ABC-123	ABC-123-002	4	2013NOV13	1	PROTOCOL	DISPOSIT	TREATMENT	Y

Proposed

Row	STUDYID	USUBJID	ASEQ	ASTDT	ASTDY	*PARQUAL*	PARAMCD	AVALC	ANL01FL
19	ABC-123	ABC-123-002	5	2013DEC01	19	INVESTIGATOR	ASSESS	SD	Y
20	ABC-123	ABC-123-002	6	2013DEC02	20	CENTRAL	ASSESS	SD	Y
21	ABC-123	ABC-123-002	7	2013DEC14	32	PROTOCOL	EVENT	MED PROCEED	
22	ABC-123	ABC-123-002	8	2013DEC27	45	INVESTIGATOR	ASSESS	PR	
23	ABC-123	ABC-123-002	9	2013DEC28	46	CENTRAL	ASSESS	PR	
24	ABC-123	ABC-123-002	10	2013DEC29	47	PROTOCOL	DISPOSIT	TREATMENT	

5.3.3 Efficacy Analysis Datasets

Once the ADEVENT dataset is created, a BDS dataset can be constructed to extract the critical data from that dataset for use in creating the tables in Section 5.2. The following ADaM dataset is an example for creating the time-to-event analysis table described above.

ADTTE Variable Metadata

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Notes
STUDYID	Study Identifier	Char		ADSL.STUDYID
USUBJID	Unique Subject Identifier	Char		ADSL.USUBJID
ASEQ	Analysis Sequence Number	Num		Sequential number for associating a record number in the ADEVENT dataset. Unique number per subject per parameter per parameter qualifier per analysis start date.
Proposed *PARQUAL*	*Parameter Qualifier*	*Char*	*INVESTIGATOR; CENTRAL; PATHOLOGIC; PROTOCOL*	*This identifies the source of the Parameter. Investigator for investigator based assessments; Central for central imaging assessments; Pathologic for an assessment by biopsy; and Protocol for events affecting assessment.*
PARAM	Parameter	Char	Progression-free Survival; Overall Survival; Duration of Response	These are the parameters used for efficacy analysis.
PARAMCD	Parameter Code	Char	PFS; OS; DOR	If progression-free survival, then set to 'PFS.' If overall survival, then set to 'OS.' If duration of response, then set to 'DOR.'
AVAL	Analysis Value	Num		The numeric value representing the time from the reference start date to the date of the analysis. (Where an analysis may be either an assessment, disposition, or event recorded as documented in ADEVENT.) PARAMCD = 'PFS': ADVENT.ASTDY when ADEVENT.ANL01FL = 'Y and ADVENT.PARAMCD = 'ASSESS' and disease progressed. PARAMCD = 'OS': ADVENT.ASTDY when ADEVENT .ANL01FL = 'Y' and ADVENT.PARAMCD = 'EVENT' and ADVENT.AVALC = 'DEATH' or when ADEVENT.ANL01FL = 'Y' and ADVENT.PARAMCD = 'DISPOSIT' and maximum ADEVENT.ASTDY. PARAMCD = 'DOR: Time from best response to when disease progressed.
CNSR	Censored	Num	1; 0	Censoring Value. Set to 1 if value is censored based on rules. PARAMCD = 'PFS': If disease did not progress, then CNSR = 1. PARAMCD = 'OS': If subject did not die, then CNSR = 1.

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Notes
				PARAMCD = 'DOR': If after having best response the disease did not progress, then CNSR = 1. Otherwise CNSR = 0.
EVNTDESC	Event or Censoring Description	Char		If an event is censored, then the reason for censoring should be described. In most cases this can be carried forward from the ADEVENT dataset. Although EVNTDESC is a permitted variable, it adds important details about censoring, so this variable to the data set always should be taken into consideration. Some examples for defining EVENTDESC: PARAMCD = 'PFS': If CNSR = 0, then EVNTDESC = 'DOCUMENTED PROGRESSION.' PARAMCD = 'OS': If CNSR = 0, then EVNTDESC = 'DEATH.' Otherwise, if CNSR = 1, then EVNTDESC = 'CENSORED AT TIME OF LAST ASSESSMENT.'
SRCDOM	Source Data	Char		The SDTM domain or ADaM dataset name that relates to the analysis value. If all events are captured in ADEVENT, then SRCDOM = 'ADEVENT.' If ADTTE is created directly from SDTM domains, then SRCDOM is equal to the domain where the data is captured.
SRCVAR	Source Variable	Char		The name of the column that relates to the analysis value. If all events are captured in ADEVENT, then SRCVAR will typically be 'ASTDY.' In some instances, such as PARAMCD = 'DOR,' there may not be one specific variable that will contain the value, so SRCVAR will be null. If ADTTE is created directly from SDTM domains, then SRCVAR is equal to the column that corresponds to the SRCDOM where the data is captured.
SRCSEQ	Source Sequence Number	Num		The sequence number of the row that relates to the analysis value. If all events are captured in ADEVENT, then SRCSEQ will typically be set to ASEQ. In some instances, such as PARAMCD = 'DOR,' there may not be one specific record that will contain the value, so SRCSEQ will be null. If ADTTE is created directly from SDTM domains, then SRCSEQ is equal to the --SEQ of the corresponding row in the SRCDOM where the data is captured.

adtte.xpt **Proposed**

Row	STUDYID	USUBJID	*PARQUAL*	PARAMCD	AVAL	CNSR	SRCSEQ
1	ABC-123	ABC-123-001	INVESTIGATOR	PFS	87	0	11
2	ABC-123	ABC-123-001	CENTRAL	PFS	88	0	12
3	ABC-123	ABC-123-002	INVESTIGATOR	PFS	19	1	5
4	ABC-123	ABC-123-002	CENTRAL	PFS	20	1	6

Given the approach of using an intermediate dataset, ADEVENT, for the collation of all information pertaining to events and censoring, additional child datasets beyond ADTTE can be created. Below is an example of an analysis dataset sourced from ADEVENT that contains parameters specific to best overall response.

ADRESP Variable Metadata – One record per subject per analysis

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Notes
STUDYID	Study Identifier	Char		ADSL.STUDYID

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Notes
USUBJID	Unique Subject Identifier	Char		ADSL.USUBJID
Proposed *PARQUAL*	*Parameter Qualifier*	*Char*	*INVESTIGATOR; CENTRAL; PATHOLOGIC; PROTOCOL z*	*This identifies the source of the Parameter. Investigator for investigator based assessments; Central for central imaging assessments; Pathologic for an assessment by biopsy; and Protocol for events affecting assessment.*
PARAM	Parameter	Char	Best Overall Response	These are the parameters used for efficacy analysis.
PARAMCD	Parameter Code	Char	BOR	For best overall response, set to 'BOR.'
AVAL	Analysis Value	Num		For parameters that have categorical response, AVAL can be used to capture the numerical ranking of the results. For example: PARAMCD = 'BOR': If AVALC = 'CR' then AVAL = 1 If AVALC = 'PR' then AVAL = 2 If AVALC = 'SD' then AVAL = 3 If AVALC = 'PD' then AVAL = 4
AVALC	Analysis Value (C)	Char		PARAMCD = 'BOR': ADEVENT.ANL01FL = 'Y and ADVENT.PARAMCD = 'ASSESS,' then set to the best response where ranking from best to worst is 'CR,' 'PR,' 'SD,' 'PD.'
SRCDOM	Source Data	Char	*	The SDTM domain or ADaM dataset name that relates to the analysis value. If all events are captured in ADEVENT, then SRCDOM = 'ADEVENT.' If ADTTE is created directly from SDTM domains, then SRCDOM is equal to the domain where the data is captured.
SRCVAR	Source Variable	Char	*	The name of the column that relates to the analysis value. If all events are captured in ADEVENT, then SRCVAR will be 'AVALC' If ADTTE is created directly from SDTM domains, then SRCVAR is equal to the column that corresponds to the SRCDOM where the data is captured.
SRCSEQ	Source Sequence Number	Num		The sequence number of the row that relates to the analysis value. If all events are captured in ADEVENT, then SRCSEQ will be set to ASEQ. If ADTTE is created directly from SDTOM domains, then SRCSEQ is equal to the --SEQ of the corresponding row in the SRCDOM where the data is captured.

adresp.xpt **Proposed**

Row	STUDYID	USUBJID	*PARQUAL*	PARAMCD	AVAL	AVALC	SRCSEQ
1	ABC-123	ABC-123-001	INVESTIGATOR	BOR	2	PR	7
2	ABC-123	ABC-123-001	CENTRAL	BOR	2	PR	8
3	ABC-123	ABC-123-002	INVESTIGATOR	BOR	3	SD	5
4	ABC-123	ABC-123-002	CENTRAL	BOR	3	SD	6

Appendices

Appendix A: Project Proposal

CFAST is proposing development of v1.0 of the CDISC Breast Cancer (BC) Therapeutic-area Data Standard. This standard would build on the existing SDTM standards and related CDASH standards to facilitate the collection and use of data relevant to BC clinical trials.

The workgroup proposes developing a CDISC therapeutic area User Guide, including concept maps, metadata, examples and controlled terminology.

The standardization effort is expected to focus on the following areas of specific interest to BC: Data to substantiate diagnosis, including H&E, ER/PR/Her2 status, as well as other key biomarkers (e.g., Ki-67, luminal A, luminal B, Oncotype DX or other gene profile assays); Medical and relevant family history (oncologic, gynecologic, and general); RECIST 1.1 tumor lesion burden and response measurements; Bone lesion assessments; Imaging modality; Key time to event analysis endpoints, including overall, progression, and disease-free survival; Treatment history type (systemic, radiological, surgical) and intent (neo/adjuvant, curative, palliative); Post-study treatment therapies type (systemic, radiological, surgical) and intent (curative, palliative); Historical/preexisting and treatment emergent adverse events using CTCAE/MedDRA terms and severity criteria; Treatment and study disposition, including reasons for discontinuation of study treatment and study participation; Cardiac function assessment; Concomitant medications, Health care resource utilization (related to both disease and supportive care) including hospitalization, intensive care, emergency visits, and hospice care.

The project is planned to begin in Q1 2014, with target completion of the BC data standard and User Guide in Q4, 2014. [dates tentative]

Appendix B: CFAST BrCa Team

Name	Institution/Organization
John Owen, Team Lead	CDISC
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Appendix C: Glossary and Abbreviations

ADaM	Analysis Data Model
Adjuvant therapy	Therapy administered to augment or stimulate other treatment modalities or to minimize or prevent disease recurrence subsequent to the main treatment plan.
AJCC	American Joint Committee on Cancer
AMA	American Medical Association
BC, BrCa	Breast cancer
BDS	Basic Data Structure
Biomedical Concept	A high-level building block of healthcare and clinical research information that encapsulates lower-level implementation details, like variables and terminologies.
BLBC	Basal-like breast cancer
BOR	Best overall response
BRCA1, BRCA2	Breast cancer 1, early onset; breast cancer 2, early onset. Sometimes called “breast cancer susceptibility” genes.
BRIDG	Biomedical Research Integrated Domain Group
CDASH	Clinical Data Acquisition Standards Harmonization Project
CDISC	Clinical Data Interchange Standards Consortium
CFAST	Coalition for Accelerating Standards and Therapies
Collected	“Collected” refers to information that is recorded and/or transmitted to the sponsor. This includes data entered by the site on CRFs/eCRFs as well as vendor data such as core lab data. This term is a synonym for “captured.”
Controlled Terminology	A finite set of values that represent the only allowed values for a data item. These values may be codes, text, or numeric. A code list is one type of controlled terminology.
C-Path	Critical Path Institute
CR	Complete response
CRF	Case report form (sometimes called a case record form). A printed, optical, or electronic document designed to record all required information to be reported to the sponsor for each trial subject.
CTCAE	Common Terminology Criteria for Adverse Events
CT/PET Scan	Computed tomography/positron emission tomography scan
CT Scan	Computed tomography scan
Curative	Treatment where the intention is to cure the disease.
DCIS	Ductal carcinoma *in situ*. A carcinoma entirely confined to the mammary ducts, with no evidence of invasion of the basement membrane. Also called intraductal carcinoma.
DFS	Disease-free survival
DNA	Deoxyribonucleic acid
Domain	A collection of observations with a topic-specific commonality about a subject.
EFS	Event-free survival
EGFR	Epidermal growth factor receptor; also called ERBB1.
ER, EsR	Estrogen receptor
FDA	U.S. Food and Drug Administration
Foundational Standards	Refers to the suite of CDISC standards that describe the clinical study protocol (Protocol), design (Study Design), data collection (CDASH), laboratory work (Lab), analysis (ADaM), and data tabulation (SDTM and SEND). See http://www.cdisc.org/ for more information on each of these clinical data standards.
H&E	Hematoxylin and eosin (stain)
HER2	Human epidermal growth factor receptor 2; also called HER2/*neu*, ERBB2.
IHC	Immunohistochemistry
Ipsilateral	Belonging to or occurring on the same side of the body.
ISH	*In situ* hybridization
ITT	Intent to treat

LCIS	Lobular carcinoma *in situ*. An adenocarcinoma entirely confined to the mammary lobules and characterized by a proliferation of monomorphic cells completely filling the lumina. The overall lobular architecture is preserved.
MedDRA	Medical Dictionary for Regulatory Activities. A global standard medical terminology designed to supersede other terminologies (such as COSTART and ICD9) used in the medical product development process.
Metastasis	A distant breast cancer recurrence; also the most dangerous type of recurrence.
MRI	Magnetic resonance imaging
NAC	Nipple-areolar complex
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI EVS	National Cancer Institute Enterprise Vocabulary Services
Neoadjuvant therapy	Treatment given as a first step to shrink a tumor prior to the main treatment.
NIH	National Institutes of Health
NSV	Non-standard variable. A variable that is not among those included in the most recent, final version of SDTM and/or CDASH.
OS	Overall survival
Palliative	Treatment where the intention is to relieve symptoms of the disease without dealing with the cause of the disease.
Patient	A recipient of medical treatment.
pCR	Pathologic complete response
PD	Progressive disease
PFS	Progression-free survival
PR, PgR	Progesterone receptor (see also Section 1.6)
PR	Partial response (see also Section 1.6)
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse-free survival
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide (for Human Clinical Trials)
Setting	Surroundings, context, or place; either physical or conceptual. Used when defining the type and intent of non-primary treatment in relation to the primary treatment.
Subject	A participant in a study.
TAUG	Therapeutic Area User Guide
TAUG-BrCa	Therapeutic Area User Guide Data Standards for Breast Cancer. This document.
TNM	A system for classifying stages of cancer based on assessments of the primary tumor, regional lymph nodes, and distant metastases. T, N, and M stand for tumor, node, and metastases, respectively.
UICC	Union for International Cancer Control
UML	Unified Modeling Language

Appendix D: Non-Standard Variables

The following table lists the NSVs used in the examples in this document, either as additional variables in sample datasets or as mapping annotations on sample CRFs, and gives their parent domain and variable-level metadata.

Parent Domain	Variable	Label	Type	Codelist/ Controlled Terms	Role	Description	Comments
CM	RSDISC	Reason for Discontinuation	text		Non-Standard Record Qualifier	The reason for ceasing (prior/concomitant) treatment.	This variable is anticipated to become standard under a future version of SDTM.
CM, PR	TRTSTT	Setting	text	(TRTRTSTT) *	Non-Standard Record Qualifier	The setting as characterized by the purpose of the study treatment in relation to the primary treatment.	Defined in the context of oncology studies; may not be appropriate for other studies.
CM, PR	TRTINT	Treatment Intent	text	(TRTINTNT) *	Non-Standard Record Qualifier	The therapeutic intent of the treatment.	
MI	PTSCL	Point Scale	text		Non-Standard Variable Qualifier of MITSTDTL	When the score is determined by a multi-point scale, how many points are on the scale.	Examples: 4-point scale, 6-point scale.
PR	CMLDOS	Cumulative Dose	float		Non-Standard Record Qualifier	For treatments with a cumulative effect, the total dose administered over a time period	May be defined by --STDTC and --ENDTC). Used instead of --DOSE.
PR	TRTBOR	Best Overall Response	text	**	Non-Standard Record Qualifier	The best outcome of the treatment.	Only applicable to prior treatments.
PR	PRLOC*n*	Procedure Location *n*	text	(LOC)	Non-Standard Record Qualifier	The *n*th anatomical location of the procedure.	Used when PRLOC = MULTIPLE; *n* stands for an integer between 1 and the maximum number of locations needed.
PR	RTTLFR	Total Fractions Count	integer		Non-Standard Record Qualifier	The cumulative dose expressed as the total number of fractions of the total intended dose.	Only applicable to prior treatments.
PR	TRTDTL	Treatment Detail	text	**	Non-Standard Variable Qualifier of PRTRT	Further description of --TRT.	In this document, this variable is used to hold the modality of the treatment.
PR	RRLTLC	Treatment-Relative Location	text	**	Non-Standard Record Qualifier	The location of the treatment's target, relative to the primary site of disease.	Defined in the context of oncology studies; may not be appropriate for other studies.
TU	LOCDTL	Location Detail	text		Non-Standard Variable Qualifier of TULOC	Specifies the exact location of the identified tumor or lesion for identification purposes.	Used when --LOC, --LAT, and --DIR are not enough to distinguish it from another tumor/lesion in the same anatomical location.
TU	PRTYP	Tumor or Lesion Presentation Type	text	(TUPRTYP) *	Non-Standard Variable Qualifier of TULOC	Specifies the disease type of the identified non-measurable tumor or lesion for identification purposes.	Used instead of --LAT/--DIR or LOCDTL when the tumor/lesion is more readily identifiable by a description than by precise anatomical location.

*(Parenthesis indicates CDISC/NCI codelist) * Codelist has been requested but not yet added to CDISC controlled terminology. ** See the CDASH metadata for a list of suggested values.*

Appendix E: Clinical Background

The presence of carcinoma is confirmed by pathology assessment of biopsy samples collected by fine needle aspiration, core needle biopsy, or excisional biopsy of a breast abnormality identified by clinical examination and imaging or mammographically.[27] A sentinel lymph node biopsy may be performed to reveal the presence of early-stage breast cancer in the location where cancerous cells are most likely to spread from a primary tumor before presenting clinically in the axial nodes.[27] In contrast, axillary lymph node dissection is performed for local disease control in patients whose cancer shows clinical or pathologic evidence of having spread to the axillary lymph node(s).

There are two types of noninvasive breast cancer: lobular carcinoma *in situ* (LCIS) and ductal carcinoma *in situ* (DCIS).

LCIS is a non-palpable breast lesion that is indicative of an increased risk for invasive breast cancer and is potentially precancerous.[28] LCIS tends to occur multi-focally and bilaterally and is more common in premenopausal women. Cases of LCIS can be observed with follow-up imaging or be excised by core needle biopsy, but treatment for LCIS is somewhat controversial. LCIS diagnoses by excisional biopsies may be upgraded to invasive cancer.[29]

DCIS refers to proliferation of mammary ductal epithelial cells that appear to be malignant but without evidence of invasion through the basement membrane.[27] The recommended patient workup for patients with suspected DCIS includes history and physical examination, bilateral diagnostic mammography, pathology review, and tumor estrogen receptor (ER) determination, with genetic counseling provided if the patient is considered at high risk for hereditary breast cancer. Magnetic resonance imaging is considered an optional test.

Primary therapy is the main treatment used to reduce or eliminate the cancer.[10] DCIS includes lumpectomy followed by clinical observation, lumpectomy with breast irradiation, or total mastectomy. The latter may be required in cases in which widespread disease (two or more quadrants) is evident and patients may be candidates for breast reconstruction. DCIS may reoccur as either DCIS or invasive breast cancer.

Adjuvant therapy is administered after primary treatment to eliminate the tumor to increase the chance of long-term survival.[10] Adjuvant therapy is typically given to patients whose disease is likely to recur. For DCIS patients with tumor ER positive status, tamoxifen has shown a role in preventing disease recurrence in the ipsilateral or contralateral breast following breast conservation surgery and irradiation.

Disease management of early-stage breast cancer (I to IIIA (T3N1M0)) aims to eradicate the primary tumor and any micro-metastatic disease. In early-stage breast cancer, a mastectomy with axillary lymph node dissection has been shown to be equivalent to breast conserving therapy with lumpectomy, axillary dissection, and whole breast radiation as primary treatment.[30] Radiation therapy is administered as part of the primary therapy in patients undergoing lumpectomy. Depending on the characteristics of the tumor, lumpectomy may not be an appropriate option, such as in the case of diffuse or widespread disease that cannot be resected with a single incision.

Neoadjuvant therapy refers to treatment administered prior to the primary therapy with the goal of shrinking the tumor.[30] In patients with human epidermal growth factor receptor 2 positive (HER2-positive) breast cancer, neoadjuvant systematic therapy may include HER2-targeted agents. Neoadjuvant endocrine therapy (tamoxifen and an aromatase inhibitor, either alone or in combination) may have a role in the management of ER-positive breast cancer in postmenopausal women.

Adjuvant therapy options for early-stage breast cancer include completion of chemotherapy (if not completed as neoadjuvant therapy), endocrine therapy in patients with ER- and/or progesterone (PR)-positive tumors, and up to one year of targeted trastuzumab therapy in HER2-positive breast cancer.[31] Radiation therapy is used in the adjuvant setting post-mastectomy in patients with node-positive disease and in node-negative tumors with a high rate of local recurrence (based on tumor size and extent of pathologic margins). In patients receiving adjuvant chemotherapy, radiation may be delayed until after chemotherapy has been completed.

Patients with locally advanced breast cancer (Stage III except for T3N1M0) have advanced breast cancer confined to the breast and regional lymph nodes.[31] Standard neoadjuvant therapy in patients with inoperable, non-inflammatory, locally advanced breast cancer includes the use of anthracycline-based chemotherapy, with or without a taxane.[32]

In patients achieving a clinical response to neoadjuvant chemotherapy, local therapy options include total mastectomy with level I/II axillary node dissection or lumpectomy with level I/II axillary node dissection, along with radiation therapy (including the supraclavicular and infraclavicular and/or internal mammary nodes and the chest wall).[31] Radiation therapy may also be given palliatively in patients not achieving a response to preoperative systemic therapy. Adjuvant therapy in patients with locally advanced breast cancer includes additional chemotherapy, endocrine therapy (in patients with ER-positive tumors), and/or targeted therapy (in patients with HER2-positive breast cancer).

Inflammatory breast cancer is rare and presents with erythema and dermal edema (*peau d'orange*) of the breast. It affects one third or more of the breast skin and is generally characterized as locally advanced. Inflammatory breast cancer is often ER-negative, but may be HER2-positive. The management of inflammatory breast cancer typically comprises neoadjuvant chemotherapy and targeted therapy (e.g., trastuzumab in HER2-positive disease and hormone therapy in ER-positive disease) followed by mastectomy with level I/II axillary lymph node dissection and radiation therapy.

Paget's disease is another rare form of breast cancer characterized by neoplastic cells in the nipple-areolar complex (NAC) that is often associated with primary breast cancer (either DCIS or invasive cancer) somewhere else in the breast. Primary therapy commonly consists of total mastectomy with axillary dissection or breast breast-conserving surgery with NAC resection, followed by whole breast irradiation. Regardless of the presence of an associated breast tumor in Paget's disease, the NAC is surgically removed with a negative margin of underlying breast tissue. Staging of the axillary lymph nodes is performed in patients with invasive breast cancer and may also be performed in patients with underlying DCIS. Systemic treatment is based on the staging and biological characteristics of the underlying tumor.

For patients with metastatic or recurrent breast cancer, disease management consists of palliative therapy and extension of overall survival. Surgery may have a role if complete local clearance of tumor can be achieved and other sites of disease are not immediately life threatening or for palliative care of a distant metastasis (where clinically indicated). Patients with bone metastases may undergo therapy with a bisphosphonate to prevent skeletal-related events (e.g., bone fractures, bone pain requiring radiation therapy, spinal cord compression, and hypercalcemia). Patients with ER- or PgR-positive breast cancer may receive endocrine therapy as initial therapy. Patients with HER2-positive breast cancer may receive a HER2-targeted agent such as trastuzumab and/or pertuzumab. Cytotoxic chemotherapy has a role in patients with hormone-negative tumors not localized to bone or soft tissue, those with symptomatic visceral metastases (regardless of hormone receptor status), and those with hormone-receptor-positive tumors refractory to endocrine therapy. The use of chemotherapy when not likely to provide an overall survival benefit must be balanced against its negative effects on quality of life. Radiation therapy has a role in the management of local or regional recurrence of breast cancer and in the palliative care of distant metastases.[32]

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