Oncology

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Link to the US NCI

Introduction

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Cancer is not just one disease but many diseases. There are more than 100 different types of cancer. Most cancers are named for the organ or type of cell in which they start - for example, cancer that begins in the colon is called colon cancer; cancer that begins in melanocytes of the skin is called melanoma.

Cancer types can be grouped into broader categories. The main categories of cancer are:

- Carcinoma - cancer that begins in the skin or in tissues that line or cover internal organs. There are a number of subtypes of carcinoma, including adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma.
- Sarcoma - cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.
- Leukaemia - a cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood.
- Lymphoma and myeloma - cancers that begin in the cells of the immune system.
- Central nervous system cancers - cancers that begin in the tissues of the brain and spinal cord.

Oncology is a branch of medicine that specialises in the diagnosis and treatment of cancer. It includes medical oncology (the use of chemotherapy, hormone therapy, and other drugs to treat cancer), radiation oncology (the use of radiation therapy to treat cancer), and surgical oncology (the use of surgery and other procedures to treat cancer).

Disease Description

All cancers begin in cells, the body's basic unit of life. To understand cancer, it's helpful to know what happens when normal cells become cancer cells.

The body is made up of many types of cells. These cells grow and divide in a controlled way to produce more cells as they are needed to keep the body healthy. When cells become old or damaged, they die and are replaced with new cells.

However, sometimes this orderly process goes wrong. The genetic material (DNA) of a cell can become damaged or changed, producing mutations that affect normal cell growth and division.

When this happens, cells do not die when they should, and new cells form when the body does not need them. The extra cells may form a mass of tissue called a tumour.

Not all tumours are cancerous; tumours can be benign or malignant.

Benign tumours aren't cancerous. They can often be removed, and, in most cases, they do not come back. Cells in benign tumours do not spread to other parts of the body. Malignant tumours are cancerous. Cells in these tumours can invade nearby tissues and spread to other parts of the body. The spread of cancer from one part of the body to another is called metastasis. Some cancers do not form tumours. For example, leukaemia is a cancer of the bone marrow and blood.

Cancer Statistics

Cancer is a leading cause of disease worldwide and GLOBOCAN estimates that 12.7 million new cancer cases occurred worldwide in 2008.2 Lung (1.6 million, 12.7% of the total for men and women), female breast (1.4 million, 10.9% of the total for women), colorectal (1.2 million, 9.7% of the total for men and women) and stomach cancers (1 million, 7.8% of the total for men and women) were the most common, accounting for more than 40% of all cases diagnosed.

Just five cancer sites –lung, female breast, colon-rectum, stomach and prostate – accounted for half (48%) of the world’s total cancer diagnoses in 2008.

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Doctors often cannot explain why one person develops cancer, and another does not. But research shows that certain risk factors increase the chance that a person will develop cancer. These are the most common risk factors for cancer:

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- Sunlight
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Many of these risk factors can be avoided. Others, such as family history, cannot be avoided. People can help protect themselves by staying away from known risk factors whenever possible.

Treatments

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Doctors also consider the patient's age and general health. Often, the goal of treatment is to cure the cancer. In other cases, the goal is to control the disease or to reduce symptoms for as long as possible. The treatment plan may change over time.

Most treatment plans include surgery, radiation therapy, or chemotherapy. Some involve hormone therapy or biological therapy. In addition, stem cell transplantation may be used so that a patient can receive very high doses of chemotherapy or radiation therapy.

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It is a copyrighted instrument, which has been translated and validated into 81 languages and is used in more than 3,000 studies worldwide. Presently QLQ-C30 Version 3.0 is the most recent version and should be used for all new studies.

It is supplemented by disease specific modules for e.g. Breast, Lung, Head & Neck, Oesophageal, Ovarian, Gastric, Cervical cancer, Multiple Myeloma, Oesophago-Gastric, Prostate, Colorectal Liver Metastases, Colorectal and Brain cancer which are distributed from the EORTC Quality of Life Department. Other disease specific modules are under development but not yet validated.

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One of the main differentiators is the role of comparator drugs in oncology trials. Placebos are never used in place of treatment when an existing standard therapy exists. If a patient is given a placebo in an oncology trial, it is always in conjunction with other approved treatments. In other therapeutic areas, it is common to have a placebo arm compared to the drug being studied.

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Phase I studies are the first test of the new treatment (new drug or new combination of drugs) and specifically in Oncology Trials are run on Patients who have Cancer and a lack of other treatment options, usually with advanced disease (e.g. metastatic cancer patients failing standard therapies) but good performance status.

The Performance Status measures the physical status of the patient; it can be used to predict how well the patient will tolerate the therapy (a very well-known prognostic factor). Two main criteria are used to evaluate the performance status:

- Karnofsky
- ECOG Performance status

Description / Rating	Fully active, able to carry out all activities without restriction	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% waking hours	Capable of only limited self-care; confined to bed or chair 50% or more of waking hours.	Completely disabled, can not carry on any self-care; totally confined to bed or chair
Karnofsky (%)	100	80 to 90	60 to 70	40 to 50	30 or less
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The primary endpoints in Phase III Oncology clinical trial design are typically based on survival-type endpoints such as overall survival, disease-free survival/ remaining recurrence-free, or progression-free survival. The aim of Phase III is to take a new treatment that has shown promising results in a Phase II setting with a smaller number of patients and compare it with the current standard treatment with a larger number of patients (hundreds to thousands), and therefore is designed to be statistically powered for comparison. Phase III clinical trials are designed to demonstrate whether the new treatment has a better clinical risk/benefit profile based on the efficacy and safety data analysis.

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This design is used to prove that the new treatment is significantly better compared to a standard.

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This design could be a special type of adaptive design and involves a number of stages within the trial separated by an interim analysis, which is used to drive the second stage of the trial design or stop the study early.

Once a drug has been proven successful in a phase III clinical trial, the researchers can submit an application for FDA approval. If data from the clinical trials meet the FDA's standards, the treatment is approved for a specific use. However, doctors sometimes prescribe a drug for a use not specified by the FDA, but rather based on studies published in peer-reviewed journals showing that the treatment works for other diseases, conditions, or symptoms; this is called "off-label" use.

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Data Challenges

Overview

The way data are collected and handled in Oncology studies is pretty standard, although there are some peculiarities.
Usually a CRF starts by collecting subject characteristics at study entry, such as Age (and/or date of birth), Sex, Race, Weight, Height, etc., followed by information about cancer diagnosis and prior cancer therapies when subjects are previously treated, for example in trials indication for 2nd or 3rd line therapy, anything else that could help in identifying the current status of the subject including the current safety profile (e.g. vital signs, laboratory, prior and current signs and symptoms, ECG, performance status, etc.).
In studies were efficacy is evaluated, periodic tumor assessment data are collected including

baseline / pre-treatment assessment.
Detailed exposure information for each experimental drugs are also collected together with repeated safety assessment. Within each 'exposure' assessment (cycles), repeated safety assessment for laboratory, ECG, vital signs, etc. could be performed (e.g. prior to drug administration, 1 hours after drug administration, 8 hours after drug administration, and so on).
It is important also to note that exposure/safety assessments usually do not have the same frequency of efficacy assessments.
Whether or not efficacy is an endpoint of the trial, follow-up information are also collected including survival status and further follow-up anti-cancer therapies.

In the introduction section categories of cancer were introduced. Another way of classifying cancer is as follows:

- Solid Tumors Cancer involving solid tumor, typically originates in a specific body organ, such a lung, breast, ovarian, etc. Types of solid tumors includes sarcomas, carcinomas, adenocarcinomas, blastomas, carcinoid tumors.
- Hematologic malignancies Arise in the blood-forming cells; typically present as systemic disease, as blood and lymphatic organs located throughout the body are affected. Types of Hematologic malignancies includes leukemias, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), multiple myeloma (MM).

More info details on the US NCI website (http://www.cancer.gov/cancertopics/types/commoncancers).

Depending on the type of cancer and sometime on the location of the cancer, data to be collected and the way they are collected may differ.

Prior Cancer History

After having identified key demographics information, the next step in collecting clinical data in oncology trial is the identification of cancer characteristics such as diagnosis and prior treatments.
As of today there is no other specific oncology SDTM standard (apart for efficacy/tumor response). Sponsors could either create ad-hoc domains or use existing standard SDTM domains. For example:

- *Prior (but also follow-up/post) anti-cancer treatments* can be mapped in CM, where anti-cancer therapies are identified using the variable CMCAT (e.g. CMCAT="Previous Anti-Cancer Therapy" or CMCAT="Further Anti-Cancer Therapy"), CMSCAT the type of anti-cancer therapy (e.g. RADIOTHERAPY), the standard CM variables to specify further details such as start/end date, dosage, unit. etc. Any other related variables if not standard in CM and not relevant for the analysis, can be mapped in a SUPPQUAL dataset (e.g. mapping to SUPPCM best overall response to prior therapies). Optionally prior surgery or any other non-drug therapies can be mapped to Medical History (MH).

- *Staging or any other variables related to the diagnosis of cancer* (especially if used as a covariate in the analysis) can be stored in Subject Characteristics (SC). For example TNM stage, histology, grading, etc.
- *Tumor History*, such as the type of cancer (e.g. Colorectal), can be also mapped in the Medical History (MH) where start date (MHSTDTC) could contain the date the cancer was histologically confirmed.

Exposure

Chemotherapy (the first systemic cancer therapy) still remains one of the main therapy which is given at some point to most of the cancer patients. Administration of 2 or more agents (cytotoxic + other) is widely used nowadays for cancer treatment (often significantly improves response and cure rates over monotherapies, that is therapy where one single drug/agent is used).
A key concept in oncology drug therapy is the concept of *Cycle*. A cycle is commonly defined as a Number of days (or weeks), e.g. 21 / 28 days (3/4 weeks), where treatment is administered on specific days (for example Day 1 to 5, 8 to 12, etc) of a cycle. When drugs are administered in combination, each drug within the combination may have a different schedule. For example drug A is administered on day 1 and 8, while drug B is administered only on day 1. The therapy, the sequence of treatment, is usually repeated (re-cycled) under certain condition usually safety and/or efficacy related. For example if a patient progressed or if the patient had severe toxic effect from which he/she did not recover, the patient is usually withdrawn from the study. In presence of toxic effects, for example a severe neutropenia with a CTCAE grade 3 or 4, the new cycle can be delayed until the toxic effect is solved (recovered). Usually one or two weeks of delay are allowed depending on the study protocol.

In most of the trials especially in phase I but also in phase II, there is no defined or specific Cycles / no. of Visits. The subject will continue the trial till the meeting of one of the trial discontinuation / treatment termination criteria as specified in the protocol.
In addition after discontinuation, same subject will enter to protocol specific follow-up period till death of the respective subject and there is no specific timeline for this.

Most of the oncology drug therapies are usually infused and in this case the patient is hospitalized. However some of the novel therapies may be also administered by means of tablets.

In describing the exposure data of a study, the concept of Dose Intensity and Relative Dose Intensity is often used together with the description of type of Treatment Modifications (for example number of cycles reduced, delayed, interrupted, overdosed).

Safety Data

Laboratory Data

Laboratory tests performed within clinical trials in oncology are used both to make immediate clinical decisions for patient's care and to define the drug profile according to the trial objectives.

Early oncology clinical trials, which are often performed in a population with advanced disease in centres of excellence serving a broad geographical area and testing toxic compounds, require frequent samplings, and laboratory results must be available to the treating physician in a very short time for quick decision making; as a consequence, the use of multiple local laboratories cannot be avoided mainly for patients convenience. The results are thus obtained using different equipments and assays which make reference to different ranges of normality and are expressed in different units. This heterogeneity implies great efforts to collect a series of different normal ranges and the need for some methods of conversion to ensure comparability of results. The list of laboratory parameters to be collected may vary from protocol to protocol, depending on the expected mechanism of action of the compound(s).

Laboratory values are often classified using the **NCI CTCAE** criteria wherever applicable. For example 'Platelets' adverse event grade 2 is defined as an observed value between 75.000/mm3 (not included) and 50.000/mm3 , regardless of the normal range of the specific laboratories.

1. Assigning NCI CTC Grades To Laboratory Results
2. Analyze This? Supporting Clinical Decisions Graphically When Not Enough Data is Available A Study Case: Challenges in NCI CTCAE Version 4 Grading
3. From Local Laboratory to Standardisation and beyond

The latest version of the NCI CTCAE criteria (currently version 4.03) is available at the US NCI website.

The Statistical Analysis Plan can be the right place where, for each collected laboratory parameter, the link to the CTCAE criteria is identified, including whether the toxicity criteria is defining either hyper or hypo toxicity or both. For example for Potassium we have both hypokalemia and hyperkalemia, this if we have to create summary statistical analysis tables by means of shit tables of baseline CTCAE value vs worst on treatment CTCAE, we will have to produce two tables, one for Potassium high values and one Potassium low value. See full details of CTCAE criteria vs laboratory parameters.

An additional analysis of laboratory data in oncology, especially for the definition of the toxicity profile (e.g. neutrophils and platelets for hematological toxicity) in the early development of cytotoxic drugs (phase I), is the evaluation of the toxic effects of the drug over time. For example a commonly analyzed parameter is the *time to nadir*, i.e. the time elapsing from treatment / cycle start to the observation of the lowest value. Similarly also time to recovery to a defined threshold is often determined; for example, if a drug is administered once every 28 days (that is the cycle duration), we may be interested to see when the most severe toxicity is to be expected (time to nadir) and what is the duration of CTCAE grade 4 toxicity (*time to recovery* to grade<=3) and of the toxicity overall (time to recovery to grade 0).

Adverse Events

Although now also adopted by other Therapeutic Area, in oncology adverse events are scored according to the guidelines provided by the National Cancer Institute: Common Terminology Criteria for Adverse Events (NCI-CTCAE). In some cases, a grade of 1 corresponds to mild, 2 to moderate, and 3 to severe. There are also two additional grades that may be assigned; 4 is a life-threatening or disabling adverse event, and 5 is a death related to the adverse event. However not all adverse events allow all five grades.

Often in oncology the following additional peculiarities in collecting adverse events are quite common:

- CTCAE Grade 5 not used – keep the worst grade and outcome=fatal
- changes in severity/grade need to be tracked e.g. each change requires closing the event with the previous grade, and opening a new event with same description, with the new grade and having start date equal to the stop date (or the day after) of the stop date of the close event
- More details in action taken (e.g dose reduction, infusion rate reduced)
- 'events' such as progression are 'obviously' not recorded as AE

In addition we may have:

- Different definitions of SAE (e.g. hospitalizations that are scheduled for trial related procedures)
- DLT variable (see Phase I studies)

When combination of drugs are used in the trial, onset, relationship and action taken are referred to each single drug. In some circumstances we may need to distinguish between Treatment Emergent flag for each drug if they are not administered simultaneously.

The Concept of Treatment Emergent Event or On-Treatment Observations

The ICH Statistical Principles for Clinical Trials (E9) defines a treatment emergent [adverse] event (TEAE) as an event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.
Although it may change between sponsors and type of studies, it is also common to define a AE being treatment emergent, if the AE occurred within a certain nr. of days (safety follow-up period) after last drug administration.
From the data collection point of view it is therefore important to be able to get the AE start date as much complete as possible (e.g. no partial date), unless the date is clearly before the 1st drug administration (e.g. previous year or previous month), data-management should make any possible effort to clarify with the investigator whether or not the AE was already present at the time of 1st drug administration.
In case AE started the same day of the 1st drug administration, it is suggested to also collect an additional field where the investigator is asked to specify whether the AE was or not already present at the time of 1st drug administration.

In trials where the investigational medical product (IMP) is tested in combination with other commercial drug (e.g. chemotherapy), you may also define TEAE with respect to the IMP when for example in the sequence of drugs used the IMP is not given as first drug (e.g. on day 2).

The same concept can be applied to any safety assessment, such as a laboratory. So for example defining Treatment Emergent Laboratory Assessment any sample collected after 1st drug administration and within 28 days from last drug administration. Usually safety outputs (e.g. a shift table of worst observed toxicity grade) are based on treatment emergent / on-treatment observations.

Despite SDTM contains some 'flag' variables to identify prior vs post treatment assessment, it is recommended to "re-derive" treatment emergent flags in ADaM by following the rules defined in the SAP. For example **TRTEMFL** in ADAE or **ONTRTFL** if using BDS structure for Laboratory.

Efficacy Data

- Tumor Assessment
- Survival Follow Up Data

Data Collection

The US NCI Enterprise Vocabular Sevices creates, compiles, and cross-maps biomedical terminology needed by NCI and its community. EVS is also collaborating with FDA and CDISC developing controlled terminology in different therapeutic area.

SDTM Data

Introduced with SDTM version 3.1.3 Oncology Disease-specific Therapeutic Area Supplement contains mapping specification for three domains:

- TU Tumor Identification
- TR Tumor Results
- RS Response

These three domains allow the mapping of tumor assessment information as per RECIST criteria.

These new standards were also presented at 2013 PHUSE SDE event in Durham.

Upcoming version 3.1.4 contains several new domains that could be used for specific or recurrent oncology type of data:

- *PR Procedures* could be used to map specific oncology procedures and/or prior prior/post anti-cancer treatments and procedures such surgeries, radiotherapies and other specific oncology drug therapies such

chemotherapies, immunotherapies, endocrine therapies, etc. Currently it is common accepted standard to map all these procedures/treatments in the CM domain.

- *SS Subject Status* could be used to stored follow-up update currently mapped either in specific ad-hoc sponsor domains or in a SUPQUAL dataset.
- *TD Trial Disease Assessments* will be a new special domain where efficacy assessment schedule could be also planned as this assessments do not have the same schedule of the standard trial visits/cycles assessments

More details on upcoming SDTM enanchements were presented at last 2013 PHUSE Basel SDE.

ADaM Data

No specific ADaM CDISC guidance have been released. However, two papers contain specific examples on how to derive and map composite time to event endpoint such Progression Free Survival.

Additional example of user implementation have been also presented at conferences: PharmaSUG 2010 CD03 ref1

Statistical Analysis

Background

- From FDA Guidance on Clinical Trial Endpoints for Cancer Clinical Trials
- Introduction to Clinical Concepts for:
  - Analysis of Response (Proportions)
  - Time to Event (Survival Analysis)
  - Adjustments for Baseline Factors
    - Logistic Regression for Best Overall Response
    - Cox Regression Models from Time to Event Endpoints

Single Arm Trials and Parallel Trials With Two or More Treatment Arms

- Analysis of Best Overall Response
- Comparison of Survival Distributions of Time of Event Endpoints (Kaplan Meier Method)

Best Overall Tumour Response for Solid Tumours

Introduction

Efficacy assessment of solid tumour cancer is usually based on imaging (E.g. CT-Scan, MRI). In the past, several attempts to define a standard criterion for solid tumour efficacy assessment were made:

- 1979: WHO Tumour Response Criteria
- 1992: SWOG revision of WHO criteria
- 2000: Response Evaluation Criteria in Solid Tumours (RECIST 1.0)
- 2008: Response Evaluation Criteria in Solid Tumours (RECIST 1.1)

These guidelines standardise solid tumour measurements and the objective assessment definition for change in tumour size.

Recist

Today, RECIST 1.1 , despite some existing criticism, is the recognised standard approach for defining tumour response for solid tumours and therefore for defining the Progression Free Survival (PFS). RECIST is a validated and « simplified » version of WHO specifically to be used in adult and paediatric cancer clinical trials (not in malignant brain tumour or malignant lymphoma studies).

MEASURABLE LESION or TARGET LESION. It can be measured in one diameter:

- Longest Diameter (LD) 20 mm or more with conventional techniques
- Longest Diameter (LD) 10 mm with spiral CT scan

RECIST recommends a maximum of 10 measurable lesions (the biggest and most suitable for repeated measures), a maximum of 5 measurable lesions per organ.

NON MEASURABLE LESION or NON TARGET LESION. All other lesions, for example:

- LD < 20 mm with conventional techniques
- LD < 10 mm with spiral CT scan
- Truly non-measurable lesions (e.g bone)

Often, having at least one measurable lesion is an eligibility criterion to enter the study. RECIST recommends performing a tumour assessment at regular intervals (usually every two cycles).

An assessment time-point is considered valid for the overall response evaluation if:

- All baseline lesions are assessed at the time point
- All lesions are assessed with the method used at baseline

Definition of Best Overall Tumour Response

The Best Overall Response (BOR) is the best response recorded from the start of the study treatment until the disease progression/recurrence:

- Complete Response (CR) upon confirmation of at least 4 weeks of 1st CR
- Partial Response (PR) upon confirmation of at least 4 weeks of the first PR
- Stable Disease (SD)
- Progressive Disease (PD)

A requirement for SD is that it should be met at least once;, no less than 6-8 weeks after the first dose of trial treatment/baseline assessment, otherwise, the best response will be Not Evaluable (NE). The criteria for confirmation of the response are summarised in the following table:

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
R	CR	CR
CR	PR	SD,PD or PR (a)
CR	SD	SD (b)
CR	PD	SD (b)
CR	NE	SD (b)
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD (b)
PR	NE	SD (b)
NE	NE	NE

Definition of Time Point Overall Response

Target Lesions Response:

- Complete Response (CR) Disappearance of all target lesions (sum of all target lesions=0)
- Partial Response (PR) >=30% decrease (vs baseline) of the sum of all target lesions dimensions
- Progressive Disease (PD) new lesions or >=20% increase (vs smallest sum of target lesions or nadir)

- Stable Disease (SD) when the sum of all target lesions does not qualify for CR/PR/PD

Non-Target Lesions Response:

- Complete Response (CR) Disappearance of all non-target lesions
- Stable Disease (SD) Persistence of non-target lesions
- Progressive Disease (PD) New lesions

The time-point overall response is then derived according to the criteria reported in the following table:

Target Lesions	Non Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/Not all evaluated	No	PR
SD	Non-PD/Not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

The objective response rate (the proportion of patients in whom a CR or PR was observed) could also be reported and analysed.