

**Cancer Association of South Africa
(CANSA)**



Research • Educate • Support

**Fact Sheet
On
Non-Hodgkin's Lymphoma**

Introduction

Lymphoma is a type of cancer involving cells of the immune system, called lymphocytes. Just as cancer represents many different diseases, lymphoma represents many different cancers of lymphocytes -- about 35 different subtypes, Lymphoma is a group of cancers that affect the cells that play a role in the immune system and primarily represents cells involved in the lymphatic system of the body (eMedicineHealth).

The Lymphatic System

The lymphatic system is an extensive drainage network that helps keep bodily fluid levels in balance and defends the body against infections. It is made up of a network of lymphatic vessels that carry lymph - a clear, watery fluid that contains protein molecules, salts, glucose, urea, and other substances - throughout the body.

The spleen, which is located in the upper left part of the abdomen under the ribcage, works as part of the lymphatic system to protect the body, clearing worn out red blood cells and other foreign bodies from the bloodstream to help fight off infection.

[Picture Credit: Lymphatic System]

One of the lymphatic system's major jobs is to collect extra lymph fluid from body tissues and return it to the blood. This process is crucial because water, proteins, and other substances are continuously leaking out of tiny blood capillaries into the surrounding body tissues. If the lymphatic system didn't drain the excess fluid from the tissues,

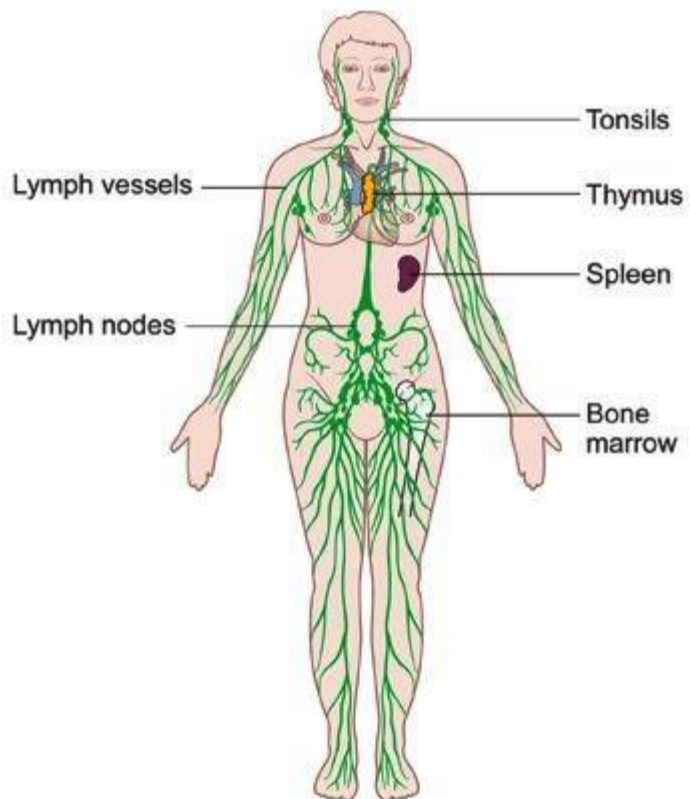


Diagram of the lymphatic system
Copyright © CancerHelp UK

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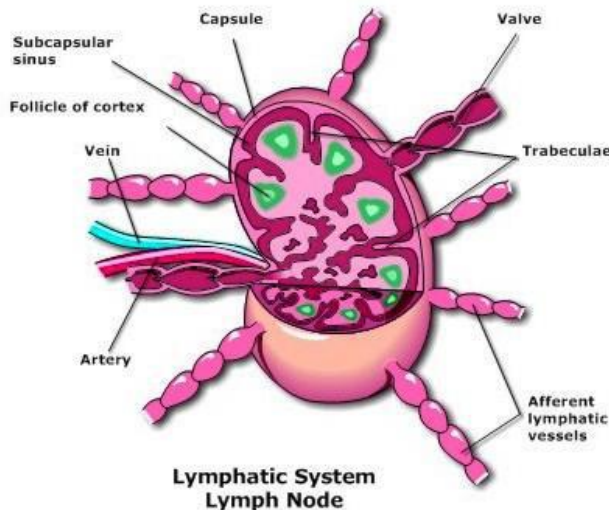
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the lymph fluid would build up in the body's tissues, and they would swell.

The lymphatic system also helps defend the body against germs like viruses, bacteria, and fungi that can cause illnesses. Those germs are filtered out in the lymph nodes, small masses of tissue located along the network of lymph vessels. The nodes house lymphocytes, a type of white blood cell. Some of those lymphocytes make antibodies, special proteins that fight off germs and stop infections from spreading by trapping disease-causing germs and destroying them.

[Picture Credit – Lymph Node]



The spleen also helps the body fight infection. The spleen contains lymphocytes and another kind of white blood cell called macrophages, which engulf and destroy bacteria, dead tissue, and foreign matter and remove them from the blood passing through the spleen (KidsHealth).

Types of Lymphoma

Lymphomas fall into one of two major categories:

- Hodgkin's lymphoma (HL, previously called Hodgkin's disease)
- Non-Hodgkin's Lymphoma (NHL, all other lymphomas)

These two types occur in the same places, may be associated with the same symptoms, and often have similar appearance on physical examination. However, they are readily distinguishable via microscopic examination.

Hodgkin's lymphoma develops from a specific abnormal B lymphocyte lineage. NHL may derive from either abnormal B or T cells and are distinguished by unique genetic markers. There are five subtypes of Hodgkin's lymphoma and about 30 subtypes of non-Hodgkin's lymphoma. Because there are so many different subtypes of lymphoma, the classification of lymphomas is complicated (it includes both the microscopic appearance as well as genetic and molecular markers).

Many of the NHL subtypes look similar, but they are functionally quite different and respond to different therapies with different probabilities of cure. HL subtypes are microscopically distinct, and typing is based upon the microscopic differences as well as extent of disease.

World Health Organization Classification System of Lymphoma Types

Over the years, various classification systems have been used to differentiate lymphoma types including the Rappaport Classification (used until the 70's), the Working Formulation,

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Page 2

the National Cancer Institute Working Formulation, and the Revised European-American Lymphoma Classification (REAL).

The WHO classification has its origins in the 1850s. The first edition, known as the International List of Causes of Death, was adopted by the International Statistical Institute in 1893. The ICD is the international standard diagnostic classification. It is used to classify diseases and other health problems recorded on many types of health and vital records including death certificates and health records. These records also provide the basis for the compilation of national mortality and morbidity statistics by WHO Member States.

The older Rappaport, Working Formulation, and REAL categories are described in a separate section for reference. This might be helpful if a patient's records state some of the classifications of older lymphoma types.

Hodgkin's lymphoma

- Lymphocytic-histiocytic predominance
- Nodular sclerosis
- Mixed cellularity
- Lymphocytic depletion
- Hodgkin's, unspecified

Follicular (nodular) non-Hodgkin's lymphoma

- Small cleaved cell, follicular
- Mixed small cleaved and large cell, follicular
- Large cell, follicular
- Other follicular non-Hodgkin's lymphoma types
- Follicular non-Hodgkin's lymphoma, unspecified
 - Nodular non-Hodgkin's lymphoma NOS

Diffuse non-Hodgkin's lymphoma

- Small cell (diffuse)
- Small cleaved cell (diffuse)
- Mixed small and large cell (diffuse)
- Large cell (diffuse)
 - Reticulum cell sarcoma
- Immunoblastic (diffuse)
- Lymphoblastic (diffuse)
- Undifferentiated (diffuse)
- Burkitt's tumour (Burkitt's lymphoma)
- Other diffuse non-Hodgkin's lymphoma types
- Diffuse non-Hodgkin's lymphoma, unspecified

Peripheral and cutaneous T-cell lymphomas

- Mycosis fungoides

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Page 3

- Sézary's disease
- T-zone lymphoma
- Lymphoepithelioid lymphoma
 - Lennert's lymphoma
- Peripheral T-cell lymphoma
- Other and unspecified T-cell lymphomas

Other and unspecified types of non-Hodgkin's lymphoma

- Lymphosarcoma
- B-cell lymphoma, unspecified
- Other specified types of non-Hodgkin's lymphoma
 - Malignant:
 - reticuloendotheliosis
 - reticulosis
 - Microglioma
- Non-Hodgkin's lymphoma, unspecified type
 - Lymphoma NOS
 - Malignant lymphoma NOS
 - Non-Hodgkin's lymphoma NOS

Malignant immunoproliferative diseases

- Waldenström's macroglobulinaemia
- Alpha heavy chain disease
- Gamma heavy chain disease
 - Franklin's disease
- Immunoproliferative small intestinal disease
 - Mediterranean disease
- Other malignant immunoproliferative diseases
- Malignant immunoproliferative disease, unspecified
 - Immunoproliferative disease NOS

Multiple myeloma and malignant plasma cell neoplasms

- Multiple myeloma
 - Kahler's disease
 - Myelomatosis
 - Excludes: solitary myeloma
- Plasma cell leukemia
- Plasmacytoma, extramedullary
 - Malignant plasma cell tumour NOS
 - Plasmacytoma NOS
 - Solitary myeloma

Lymphoid leukaemia

- Acute lymphoblastic leukaemia

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Page 4

- Excludes: acute exacerbation of chronic lymphocytic leukaemia
- Chronic lymphocytic leukaemia
- Subacute lymphocytic leukaemia
- Prolymphocytic leukaemia
- Hairy-cell leukaemia
- Leukaemic reticuloendotheliosis
- Adult T-cell leukaemia
- Other lymphoid leukaemia
- Lymphoid leukaemia, unspecified

Myeloid leukaemia

- Includes:
 - granulocytic
 - myelogenous
- Acute myeloid leukaemia
 - Excludes: acute exacerbation of chronic myeloid leukaemia
- Chronic myeloid leukaemia
- Subacute myeloid leukaemia
- Myeloid sarcoma
 - Chloroma
 - Granulocytic sarcoma
- Acute promyelocytic leukaemia
- Acute myelomonocytic leukaemia
- Other myeloid leukaemia
- Myeloid leukaemia, unspecified

Monocytic leukaemia

- Includes: monocytoid leukaemia
- Acute monocytic leukaemia
 - Excludes: acute exacerbation of chronic monocytic leukaemia
- Chronic monocytic leukaemia
- Subacute monocytic leukaemia
- Other monocytic leukaemia
- Monocytic leukaemia , unspecified

Other leukaemias of specified cell type

- Acute erythraemia and erythroleukaemia
 - Acute erythraemic myelosis
 - Di Guglielmo's disease
- Chronic erythraemia
 - Heilmeyer-Schöner disease
- Acute megakaryoblastic leukaemia
 - leukaemia :
 - megakaryoblastic (acute)
 - megakaryocytic (acute)
- Mast cell leukaemia

- Acute panmyelosis
- Acute myelofibrosis
- Other specified leukaemia s
 - Lymphosarcoma cell leukaemia

Leukaemia of unspecified cell type

- Acute leukaemia of unspecified cell type
 - Blast cell leukaemia
 - Stem cell leukaemia
- Chronic leukaemia of unspecified cell type
- Subacute leukaemia of unspecified cell type
- Other leukaemia of unspecified cell type
- leukaemia , unspecified

Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue

- Letterer-Siwe disease
 - Nonlipid:
 - reticuloendotheliosis
 - reticulosis
- Malignant histiocytosis
 - Histiocytic medullary reticulosis
- Malignant mast cell tumour
 - Malignant:
 - mastocytoma
 - mastocytosis
 - Mast cell sarcoma
 - Excludes: mast cell leukaemia
 - mastocytosis (cutaneous)
- True histiocytic lymphoma
- Other specified malignant neoplasms of lymphoid, haematopoietic and related tissue
- Malignant neoplasm of lymphoid, haematopoietic and related tissue, unspecified
(Lymphomainfo.net)

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma is cancer of the lymphoid tissue, which includes the lymph nodes, spleen, and other organs of the immune system.

Causes, Incidence, and Risk Factors for Non-Hodgkin's Lymphoma

White blood cells called lymphocytes are found in lymph tissues. They help prevent infections. Most Non-Hodgkin's Lymphomas (NHL) start in a type of white blood cells called B lymphocytes, or B cells.

Some of the Known Risk Factors for Non-Hodgkin's Lymphoma include:

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- Age - Non-Hodgkin's lymphoma can develop in people of all ages, including children, it is most common in adults. The most common types of NHL usually appear in people in their 60s and 70s.
- Sex - In general, NHL is more common in men than in women.
- Race - Overall, the risk for NHL is slightly higher in Caucasians than in African-Americans and Asian Americans.
- Family History - People who have close family relatives who have developed NHL may be at increased risk for this cancer. However, no definitive hereditary or genetic link has been established.
- Infections - Viral or bacterial infections may play a role in some lymphomas. These include:
 - Epstein-Barr virus (EBV), the cause of mononucleosis, is highly associated with Burkitt's lymphoma and NHLs associated with immunodeficiency diseases. It is also a risk factor for Hodgkin's disease.
 - The human immunodeficiency virus (HIV), which causes AIDS, increases the risk for Burkitt lymphoma and diffuse large B-cell lymphoma
 - The hepatitis C virus (HCV) may increase the risk for certain types of lymphomas.
 - The *Helicobacter pylori* bacterium, which causes stomach ulcers, is associated with increased risk for mucosa-associated lymphoid tissue lymphomas (MALT). (The use of antibiotics to get rid of the bacteria may cause remission in some patients who have an early stage form of lymphoma in an early stage.)
- Immune System Deficiency Disorders - Patients with diseases or conditions that affect the immune system may be at higher risk for lymphomas:
 - HIV-positive patients and those with full-blown AIDS are at higher risk for NHL, and the disease is more likely to be widespread in these patients than in those without the immune disease. Most AIDS-related NHLs are high-grade lymphomas.
 - People who have organ transplants are at higher risk for NHL, probably due to multiple factors, including the drugs used to suppress the immune system and the transplanted organ itself.
 - Patients who have had high-dose chemotherapy with stem-cell transplantation are at higher risk.
- Other immunodeficiency syndromes that put people at risk for NHL include Chediak-Higashi syndrome, ataxia-telangiectasia, B-cell lymphoproliferative syndrome, Bruton agammaglobulinemia, common variable immunodeficiency, and Wiskott-Aldrich syndrome.
- Autoimmune Disorders - Patients with a history of autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus, Hashimoto's thyroiditis, Crohn's disease, and Sjogren syndrome, are at an increased risk for certain NHLs, such as marginal zone lymphomas.
- Chemical Exposure - Overexposure to a number of industrial and agricultural chemicals (such as pesticides, herbicides, and petrochemicals) has been frequently linked to an increased risk for lymphomas. The data, however, are not consistent.

Researchers are also investigating whether some chemotherapy drugs may increase the risk for later developing non-Hodgkin's lymphoma. At this point, it is not clear whether these drugs or the other cancers themselves increase risk. Other types of drugs, such as tumour necrosis factor (TNF) inhibitors that are used to treat autoimmune disorders, are also being studied as possible risk factors for lymphomas.

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Page 7

Radiation Exposure - People who have had radiation treatment for cancer, such as Hodgkin's lymphoma, appear to have an increased risk for later developing non-Hodgkin's lymphoma. The risk may be higher for patients treated with both chemotherapy and radiation.

Survivors of nuclear reactor disasters have an increased risk of developing NHL, as well as other types of cancers.

- Lifestyle Factors - Lifestyle does not seem to be a major risk factor for NHL. Some studies have suggested that obesity may increase risk, but this association is not definite. Other studies have investigated the role of diet. Although some research has indicated an increased risk for diets high in consumption of red meat and lower risk for diets high in vegetables, for the most part a strong association remains speculative. There is no evidence that smoking increases the risk for NHL itself, although it has been linked with high-grade and follicular NHLs in people with lymphoma.

There are many different types of non-Hodgkin's lymphoma (NHL). It is grouped according to how fast the cancer spreads.

- The cancer may be low grade (slow growing), intermediate grade, or high grade (fast growing). Burkitt's lymphoma is an example of a high-grade lymphoma. Follicular lymphoma is a low-grade lymphoma.
- The cancer is further grouped by how the cells look under the microscope, for example, if there are certain proteins or genetic markers present.

Incidence of Non-Hodgkin's Lymphoma in South Africa

According to the National Cancer Registry (2013) the following number of Non-Hodgkin's Lymphoma cases were histologically diagnosed in South Africa during 2013:

Group - Males 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	882	1:221	2,45%
Asian males	25	1:241	2,97%
Black males	516	1:316	4,79%
Coloured males	88	1:192	2,12%
White males	254	1:123	1,26%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	802	1:327	2,19%
Asian females	21	1:296	1,98%
Black females	471	1:461	3,02%
Coloured females	76	1:267	1,87%
White females	234	1:163	1,47%

The frequency of histologically diagnosed cases of Non-Hodgkin's Lymphoma in South Africa for 2013 was as follows (National Cancer Registry, 2013):

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Group - Males 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	29	46	152	199	172	144	85	40
Asian males	0	0	1	7	7	5	2	1
Black males	25	30	126	142	105	40	18	5
Coloured males	2	4	7	14	18	27	8	4
White males	2	9	15	32	38	67	55	28

Group - Females 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	24	54	164	165	124	125	81	52
Asian females	1	0	0	3	2	7	4	1
Black females	16	47	140	122	61	39	16	10
Coloured females	2	3	10	12	18	13	11	4
White females	5	2	12	23	38	60	48	36

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Symptoms of Non-Hodgkin's Lymphoma

Symptoms depend on what area of the body is affected by the cancer and how fast the cancer is growing. Symptoms may include:

[Picture Credit: Non-Hodgkin's Lymphoma]

- Night sweats (soaking the bedsheets and pyjamas even though the room temperature is not too hot)
- Fever and chills that come and go
- Itching
- Swollen lymph nodes in the neck, underarms, groin, or other areas
- Weight loss
- Coughing or shortness of breath may occur if the cancer affects the thymus gland or lymph nodes in the chest, which may put pressure on the windpipe (trachea) or other airways.
- Some patients may have abdominal pain or swelling, which may lead to a loss of appetite, constipation, nausea, and vomiting.
- If the cancer affects cells in the brain, the person may have a headache, concentration problems, personality changes, or seizures.



Signs and Tests for Non-Hodgkin's Lymphoma

The doctor will perform a physical exam and check body areas with lymph nodes to feel if they are swollen.

The disease may be diagnosed after:

- Biopsy of suspected tissue, usually a lymph node biopsy
 - Bone marrow biopsy
- Other tests that may be done include:
- Blood test to check protein levels, liver function, kidney function, and uric acid level
 - Complete blood count (CBC)
 - CT scans of the chest, abdomen and pelvis
 - Gallium scan
 - PET (positron emission tomography) scan

Treatment of Non-Hodgkin's Lymphoma

Treatment depends on:

- The type of lymphoma
- The stage of the cancer when you are first diagnosed
- Your age and overall health
- Symptoms, including weight loss, fever, and night sweats

Common treatments include:

- Radiation therapy may be used for disease that is confined to one body area.
- Chemotherapy is the main type of treatment. Most often, multiple different drugs are used in combination together.
- Another drug, called rituximab (Rituxan), is often used to treat B-cell non-Hodgkin's lymphoma.
- Radioimmunotherapy may be used in some cases. This involves linking a radioactive substance to an antibody that targets the cancerous cells and injecting the substance into the body.
- People with lymphoma that returns after treatment or does not respond to treatment may receive high-dose chemotherapy followed by a bone marrow transplant (using stem cells from the patient).

Additional treatments depend on other symptoms. They may include:

- Transfusion of blood products, such as platelets or red blood cells
- Antibiotics to fight infection, especially if a fever occurs

In 2017 the Food and Drug Administration (FDA) has approved Rituxan Hycela (rituximab and hyaluronidase human) for subcutaneous injection for the treatment of Follicular Lymphoma and Diffuse Large B-cell Lymphoma.

In the treatment of Follicular Lymphoma (FL), Rituxan Hycela is indicated for relapsed or refractory FL as a single agent; for previously untreated FL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy; and for non-progressing (including stable disease) FL as a single agent after first-line cyclophosphamide, vincristine, and prednisone chemotherapy.

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Page 10

Rituxan Hycela is also indicated for previously untreated Diffuse Large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone or other anthracycline-based chemotherapy regimens and for previously untreated and previously treated chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide.
(MPR).

Expectations (Prognosis) of Non-Hodgkin's Lymphoma

Low-grade non-Hodgkin's lymphoma usually cannot be cured by chemotherapy alone. However, the low-grade form of this cancer progresses slowly, and it may take many years before the disease gets worse or even requires any treatment. Chemotherapy can often cure many types of high-grade lymphoma. However, if the cancer does not respond to chemotherapy drugs, the disease can cause rapid death.

Complications of Non-Hodgkin's Lymphoma

Complications include:

- Autoimmune haemolytic anaemia
- Infection
- Side effects of chemotherapy drugs

(University of Maryland Medical Center; PubMed; American Cancer Society)

Relationship of Staging Systems – Hodgkin Lymphoma and Non-Hodgkin Lymphomas

Description of Extent (Based on Ann Arbor Staging Systems)	Summary Stage	Ann Arbor Staging*	AJCC Staging Stage**
Involvement of a single lymph node region	Localised	I	I
A single extralymphatic organ or site	Localised	Ie	Ie
Involvement of more than one lymphatic region on only one side of the diaphragm	Regional NOS	II	II
Localised involvement of one extralymphatic organ or site and its regional lymph nodes with or without other nodes on the same side of the diaphragm	Regional NOS	IIE	IIE
Involvement of more than one lymphatic region on only one side of the diaphragm plus involvement of the spleen	Distant	IIS	IIS
Involvement of lymph node regions on both sides of the diaphragm	Distant	III	III
Involvement of lymph node regions on both sides of the diaphragm plus localised involvement of an extralymphatic organ or site	Distant	IIIE	IIIE
Involvement of lymph node regions on both sides of the diaphragm plus involvement of the spleen	Distant	IIIS	IIIS
Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Organs considered distant include liver, bone, bone marrow, lung and/or pleura and kidney	Distant	IV	IV
Isolated extralymphatic organ involvement with distant (non-regional) nodal involvement	Distant	IV	IV

(National Cancer Institute)

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About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians,

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Page 12

pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different “phase” in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or “control” interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.

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November 2017

Page 15

- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by

patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care. (National Cancer Institute).

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSAs) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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Lymphatic System

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Lymph Node

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November 2017

Page 18

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