Cancer Association of South Africa (CANSA)

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Fact Sheet
On
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]

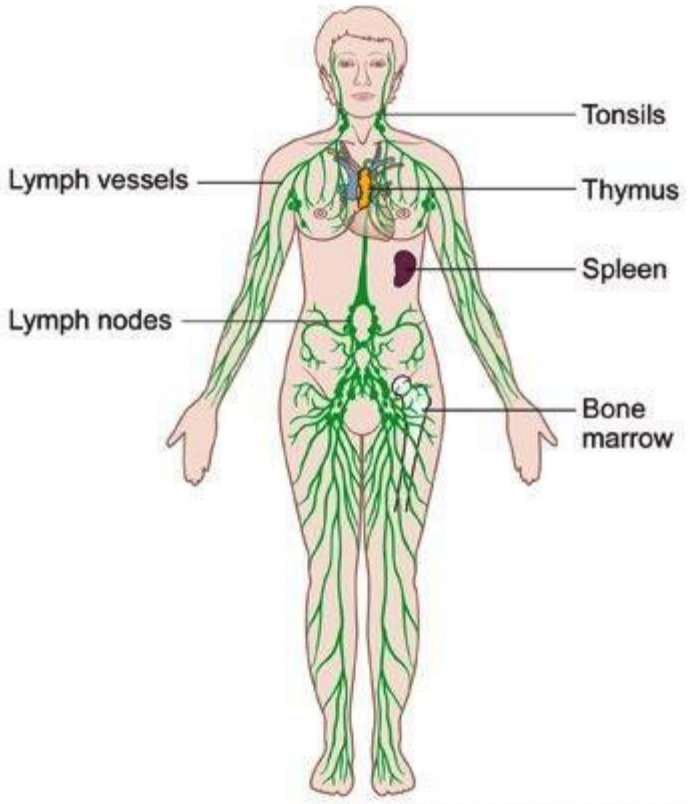

Diagram of the lymphatic system
Copyright © CancerHelp UK

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 did not drain the excess fluid from the tissues,

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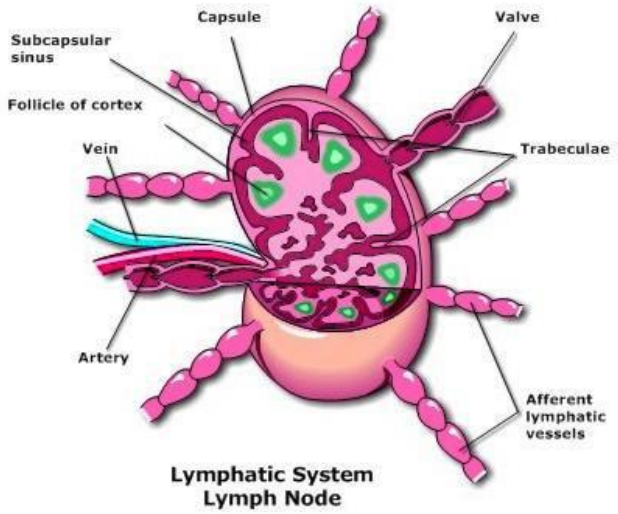
the lymph fluid would build up in the body's tissues, and the tissue would swell.

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,

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

- 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

    - 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)

Hodgkin's Lymphoma

Hodgkin's lymphoma is a cancer of lymph tissue found in the lymph nodes, spleen, liver, bone marrow, and other sites.

Incidence Hodgkin's Lymphoma in South Africa

According to the National Cancer Registry (2013) the following number of 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	273	1:994	0,76%
Asian males	11	1:809	1,36%
Black males	170	1:1 433	1,58%
Coloured males	34	1:804	0,81%
White males	59	1:468	0,29%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	184	1:1 848	0,50%
Asian females	10	1:809	0,92%
Black females	121	1:2 314	0,77%
Coloured females	19	1:1 996	0,47%
White females	35	1:827	0,22%

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

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	47	48	62	50	35	17	8	1
Asian males	0	1	3	2	2	2	0	1
Black males	31	33	42	33	19	5	0	0
Coloured males	7	3	6	7	6	1	1	0
White males	7	10	10	6	8	9	6	0

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	18	48	53	34	16	9	4	0
Asian females	1	0	4	1	1	2	0	0
Black females	9	32	36	24	10	3	0	0
Coloured females	3	4	5	2	3	0	1	0
White females	5	9	7	5	1	3	3	0

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.

Causes and Risk Factors of Hodgkin's Lymphoma

The cause of Hodgkin's Lymphoma is not known. Hodgkin's lymphoma is most common among people ages 15 - 35 and 50 - 70. Past infection with the Epstein-Barr virus (EBV) is thought to contribute to some cases. Patients with HIV infection are more at risk than the general population.

Risk Factors

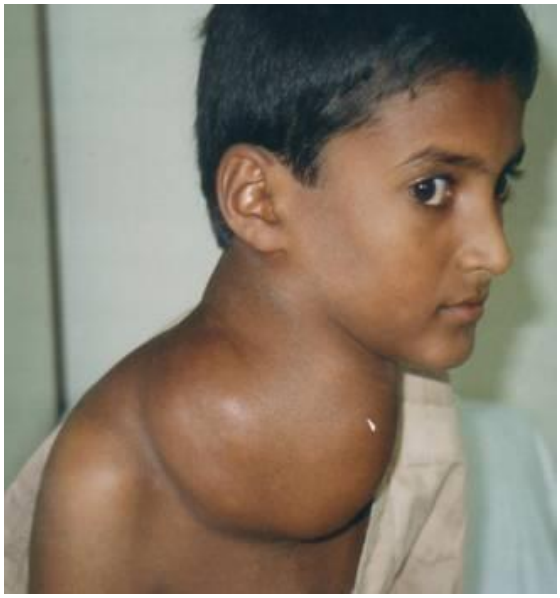
Factors that increase the risk of Hodgkin's lymphoma include:

- Age - Hodgkin's lymphoma is most often diagnosed in people between the ages of 15 and 35, as well as those older than 55.
- A family history of lymphoma - Anyone with a brother or a sister who has Hodgkin's lymphoma or non-Hodgkin's lymphoma has an increased risk of developing Hodgkin's lymphoma. Studies also show up to a seven-fold increased risk in people with a parent or sibling diagnosed with Hodgkin's lymphoma or with any blood or lymphatic cancer
- Sex - Males are slightly more likely to develop Hodgkin's lymphoma.
- Past Epstein-Barr infection - People who have had illnesses caused by the Epstein-Barr virus, such as infectious mononucleosis, are more likely to develop Hodgkin's lymphoma than are people who haven't had Epstein-Barr infections.

- A weakened immune system - Having a compromised immune system, such as from HIV/AIDS or from having an organ transplant requiring medications to suppress the immune response, increases the risk of Hodgkin's lymphoma.

Symptoms of Hodgkin's Lymphoma
The following symptoms may present:

- Fatigue
- Fever and chills that come and go
- Itching all over the body that cannot be explained
- Loss of appetite
- Soaking night sweats
- Painless swelling of the lymph nodes in the neck, armpits, or groin (swollen glands)
- Weight loss that cannot be explained



[Picture Credit: Hodgkin's Lymphoma]

Other symptoms that may occur with this disease:

- Coughing, chest pains, or breathing problems if there are swollen lymph nodes in the chest
- Excessive sweating
- Pain or feeling of fullness below the ribs due to swollen spleen or liver
- Pain in lymph nodes after drinking alcohol
- Skin blushing or flushing

Note: Symptoms caused by Hodgkin's lymphoma may also occur with other conditions. Talk to your doctor about the meaning of your specific symptoms.

Signs and tests
The first sign of Hodgkin's lymphoma is often a swollen lymph node, which appears without a known cause. The disease can spread to nearby lymph nodes. Later it may spread to the spleen, liver, bone marrow, or other organs.

The disease may be diagnosed after:

- Biopsy of suspected tissue, usually a lymph node biopsy
- Bone marrow biopsy

If tests reveal that the patient has Hodgkin's lymphoma, more tests will be done to see if the cancer has spread. This is called staging. Staging helps guide treatment and follow-up, and provides some idea of what to expect in the future.

The following procedures will usually be done:

- Blood chemistry tests including protein levels, liver function tests, kidney function tests, and uric acid level
- Bone marrow biopsy
- CT scans of the chest, abdomen, and pelvis
- Complete blood count (CBC) to check for anaemia and white blood count
- PET scan

Some people may need abdominal surgery to take out a piece of the liver and remove the spleen. However, because the other tests are now so good at detecting the spread of Hodgkin's lymphoma, this surgery is usually not needed.

Staging of Hodgkin's Lymphoma

The doctor considers the following to determine the stage of Hodgkin's lymphoma:

- The number of lymph nodes that have Hodgkin lymphoma cells
- Whether these lymph nodes are on one or both sides of the diaphragm (see picture)
- Whether the disease has spread to the bone marrow, spleen, liver, or lung.

The stages of Hodgkin lymphoma are as follows:

Stage I: the lymphoma cells are in one lymph node group (such as in the neck or underarm). Or, if the lymphoma cells are not in the lymph nodes, they are in only one part of a tissue or an organ (such as the lung).

Stage II: the lymphoma cells are in at least two lymph node groups on the same side of (either above or below) the diaphragm. Or, the lymphoma cells are in one part of a tissue or an organ and the lymph nodes near that organ (on the same side of the diaphragm). There may be lymphoma cells in other lymph node groups on the same side of the diaphragm.

Stage III: the lymphoma cells are in lymph nodes above and below the diaphragm. Lymphoma also may be found in one part of a tissue or an organ (such as the liver, lung, or bone) near these lymph node groups. It may also be found in the spleen.

Stage IV: lymphoma cells are found in several parts of one or more organs or tissues. Or, the lymphoma is in an organ (such as the liver, lung, or bone) and in distant lymph nodes.

Recurrent: the disease returns after treatment.

In addition to these stage numbers, the doctor may also describe the stage as A or B:

A: the patient did not experience any weight loss, drenching night sweats, or fevers.

B: the patient has experienced weight loss, drenching night sweats, or fevers.

The Ann Arbor Staging System

The traditional staging for Hodgkin lymphoma and non-Hodgkin lymphoma was initially presented at the Ann Arbor Symposium on Staging of Hodgkin lymphoma, April, 1971. For the Ann Arbor System, clinical staging includes all of the non-invasive procedures;

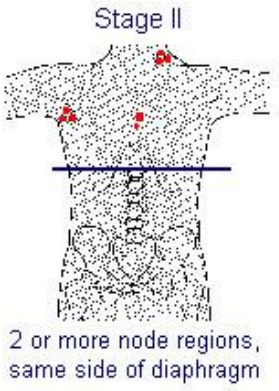
pathologic staging is based on findings made as a result of invasive procedures such as laparotomy (a surgical procedure involving an incision through the abdominal wall to gain access into the abdominal cavity) or mediastinotomy (a surgical procedure involving an incision through the chest wall to gain access into the mediastinum or area between the lungs).

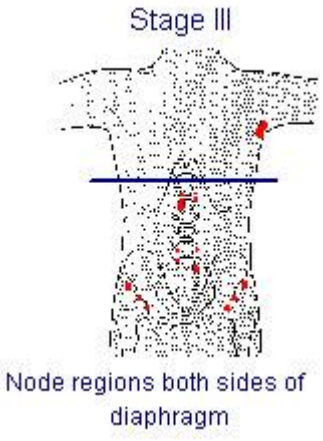
Definitions for TNM clinical staging and pathologic staging using the Ann Arbor system are the same. T, N, and M elements are not applicable to this staging system.

Criteria for TNM Clinical Staging: Physical examination and history; urinalysis; chest x-ray; blood chemistries; bilateral bone marrow biopsies, plus lymphangiogram, abdominal CT scan. Also (optional, depending on previous findings) bone imaging, technetium scans, CT scans, chest tomography, lumbar puncture, ultrasound, gallium scans (a test that uses a radioactive material called gallium to look for swelling (inflammation), infection, or cancer in the body), liver/spleen scan. Criteria for TNM Pathologic Staging: All of the clinical studies above, plus biopsy of accessible extranodal primary site(s). Staging laparotomy (including splenectomy (surgical removal of the spleen), wedge liver biopsy, and multiple lymph node biopsies) is not required but may be used for additional staging information if indicated. Otherwise, liver biopsy, or other biopsies to determine distant metastases.

The Cotswolds Modifications of the Ann Arbor Staging Classification

- Add a suffix X to designate bulky disease (defined as a mass of nodes with one diameter of > 10 cm or a mediastinal mass of > 1/3 of the transthoracic {mediastinal} width)
- The number of anatomic regions involved should be indicated by a subscript (e.g., II3)
- Stage III may be subdivided into:
    - III1 with or without splenic, hilar, coeliac, or portal nodes
    - III2 with para-aortic, iliac, or mesenteric nodes
- Staging should be identified as clinical stage (CS) or pathologic stage (PS)
- A new category of response to therapy, unconfirmed/uncertain complete remission, should be introduced because of the persistent radiologic abnormalities of uncertain significance.





Node regions both sides of diaphragm

Diffuse extralymphatic involvement

Treatment of Hodgkin's Lymphoma

Treatment of Hodgkin's Lymphoma depends on the following:

- The type of Hodgkin's lymphoma (most people have classic Hodgkin's lymphoma)
- The stage (where the disease has spread)
- Whether the tumour is more than 10 cm wide
- The age and other medical issues
- Other factors, including weight loss, night sweats, and fever

Tests will be done to see if the cancer has spread. This is called staging. Staging helps guide future treatment and follow-up and gives one some idea of what to expect in the future. Staging is needed to determine the treatment plan. Stages of Hodgkin's lymphoma range from I to IV. The higher the staging number, the more advanced the cancer.

Treatment depends on the patient's age and stage of the cancer.

Stage I and Stage II (limited disease) - can be treated with radiation therapy, chemotherapy, or both

Stage III - is treated with chemotherapy alone, or a combination of radiation therapy and chemotherapy

Stage IV (extensive disease) - is most often treated with chemotherapy alone

People with Hodgkin's lymphoma that returns after treatment or does not respond to the first treatment may receive high-dose chemotherapy. That is followed by an autologous stem cell transplant (using stem cells from the patient him/herself).

What other treatments one has depend on the patient's symptoms, but may include:

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

Targeted Therapy - newer drugs that work differently from standard chemo drugs are now being studied as well. These are known as *targeted therapy* drugs.

For example, drugs known as *mTOR inhibitors* (such as sirolimus, temsirolimus, and everolimus) have shown some promise in early clinical studies against relapsed Hodgkin's lymphoma. Drugs called *histone deacetylase (HDAC) inhibitors*, such as panobinostat and vorinostat, have also shown some early promise.

Other drugs being studied include lenalidomide (Revlimid®) and bortezomib (Velcade®). These drugs are more often used to treat multiple myeloma and some non-Hodgkin's lymphomas, but they may prove to be useful in Hodgkin's lymphoma as well.

Some newer targeted drugs, such as PLX3397, might affect the other cells in Hodgkin's lymphoma tumours, rather than the cancer cells themselves. These other cells actually make up much of the Hodgkin's lymphoma tumours and are thought to help the cancer cells grow. Research on these types of drugs is still in early stages.

Monoclonal antibodies - antibodies are proteins normally made by the immune system to help fight infections. Each antibody attacks only a specific target (usually a protein on the surface of an unwanted cell). Monoclonal antibodies (mAbs) are man-made versions of these immune system proteins. Some can kill cancer cells by themselves. Others have radioactive molecules or cell poisons attached to them, which help kill the cancer cells. An advantage of these drugs is that they seem to target lymphoma cells while having fewer side effects than standard chemotherapy drugs. They may be used alone or combined with chemotherapy.

Some mAbs, such as brentuximab vedotin (Adcetris) and rituximab (Rituxan), are already being used to treat Hodgkin's lymphoma in some situations. Researchers are now looking to see if these drugs might be useful in other situations. For example, brentuximab is now being studied to see if it might be helpful earlier in the course of the disease. And studies are now being done to see if rituximab can help treat classic forms of Hodgkin's lymphoma as well as the nodular lymphocyte predominant type.

Many newer mAbs are now being studied as well.

Immunotherapy - also called biologic therapy, is designed to boost the body's natural defenses to fight the cancer. It uses materials made either by the body or in a laboratory to improve, target, or restore immune system function. Some treatments involve the use of antibodies that attach to proteins on the surface of cancer cells. Other antibodies are used to direct drugs to the cancer cells.

One type of immunotherapy currently being studied is a class of drugs known as PD-1 inhibitors. The PD-1 pathway may be critical in the immune system's ability to control cancer growth. Blocking this pathway with PD-1 and PD-L1 antibodies may help stop or slow cancer growth. Although it is still early in development, these new therapies show considerable promise for the treatment of recurrent Hodgkin's lymphoma.

Gene profiling - some researchers are looking at the specific genes and proteins that are found in Hodgkin's lymphoma. These genes and proteins provide more information about the

behaviour of Hodgkin's lymphoma, which may help better target the lymphoma with chemotherapy or immunotherapy.

Other treatments - stem cell transplantation is being studied in combination with chemotherapy and immunotherapy regimens for new or recurrent Hodgkin's lymphoma. Mini-allogeneic, also called non-myeloablative or reduced intensity transplant, and allogeneic transplantation are being tested in combination with chemotherapy and immunotherapy for new or recurrent Hodgkin lymphoma.

Reducing treatment intensity - some earlier stage Hodgkin's lymphoma subtypes have such high cure rates that less intense treatment plans are being tested. These lower intensity plans reduce the use of radiation therapy or decrease the amount of chemotherapy. The goal is to effectively treat the lymphoma with fewer long-term side effects. Often, patients receive a PET scan after a short course of chemotherapy to help define these treatment reductions.

Palliative care - clinical trials are underway to find better ways of reducing symptoms and side effects of current Hodgkin's lymphoma treatments in order to improve patients' comfort and quality of life.
(American Cancer Society; WebMD; Cancer.Net).

Chemotherapy - Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly.

First-Line Therapy - Stage IA, IIA Favourable

Regimen:	**Dosing:**
Doxorubicin + Bleomycin + Vinblastine + Dacarbazine (ABVD)2	**Days 1 and 15**: Doxorubicin 25mg/m^2 IV push + bleomycin 10units/m^2 IV push + vinblastine 6mg/m2 IV over 5–10 minutes + dacarbazine 375mg/m^2 IV over 60 minutes. Repeat cycle every 4 weeks for 2–4 cycles followed by radiation therapy (Category 1)
Doxorubicin + Vinblastine + Mechlorethamine + Etoposide + Vincristine + Bleomycin + Prednisone (Stanford V)	**Days 1 and 15**: Doxorubicin 25mg/m^2 IV push + vinblastine 6mg/m2 IV over 5–10 minutes **Day 1**: Mechlorethamine 6mg/m^2 IV push **Days 8 and 22**: Vincristine 1.4mg/m2 (maximum 2mg) IV over 5–10 minutes + bleomycin 5units/m^2 IV push **Days 15 and 16**: Etoposide 60mg/m^2 IV over 60 minutes **Days 1–28**: Prednisone 40mg/m^2 orally every other day. Taper prednisone dose by 10mg every other day beginning Day 15 of Cycle 2. Repeat cycle every 4 week for 2 cycles followed by radiation therapy, optimally within 3 weeks of chemotherapy completion

First-Line Therapy - Stage I–II Unfavourable (Bulky or Non-bulky Disease)

Regimen:	**Dosing:**
Doxorubicin + Bleomycin + Vinblastine + Dacarbazine (ABVD)	**Days 1 and 15**: Doxorubicin 25mg/m^2 IV push + bleomycin 10units/m^2 IV push + vinblastine 6mg/m^2 IV over 5–10 minutes + dacarbazine 375mg/m^2 IV over 60 minutes. Bulky or non-bulky disease: Repeat cycle every 4 weeks for 4-6 cycles with or without subsequent radiation therapy (category 1 for bulky disease); Or for selected patients younger than 6o years, repeat for 2 cycles, following 2 cycles of escalated BEACOPP, with or without subsequent radiation therapy.
Doxorubicin + Vinblastine + Mechlorethamine + Etoposide + Vincristine + Bleomycin + Prednisone (Stanford V)	**Days 1 and 15**: Doxorubicin 25mg/m^2 IV push + vinblastine 6mg/m^2 IV over 5–10 minutes **Day 1**: Mechlorethamine 6mg/m^2 IV push **Days 8 and 22**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5–10 minutes + bleomycin 5units/m^2 IV push **Days 15 and 16**: Etoposide 60mg/m^2 IV over 60 minutes **Days 1–28**: Prednisone 40mg/m^2 orally every other day. Taper prednisone dose by 10mg every other day beginning Day 15 of Cycle 3. Repeat cycle every 4 weeks for 3 cycles with or without subsequent radiation therapy.
Bleomycin + Etoposide + Doxorubicin + Cyclophosphamide + Vincristine + Procarbazine + Prednisone (Escalated BEACOPP)	**Day 1**: Cyclophosphamide 1,250mg/m^2 IV over 60 minutes + doxorubicin 35mg/m^2 IV push **Days 1–3**: Etoposide 200mg/m^2 IV over 2 hours **Days 1–7**: Procarbazine 100mg/m^2 orally. **Day 8**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5–10 minutes + bleomycin 10units/m^2 IV push. **Days 1–14**: Prednisone 40mg/m^2 orally daily. Repeat cycle every 3 weeks for 2 cycles followed by ABVD and then by radiation therapy.

(Cancer Therapy Advisor).

First-Line Therapy – Stage III – IV

Regimen:	**Dosing:**
Doxorubicin + Bleomycin + Vinblastine + Dacarbazine (ABVD)	**Days 1 and 15**: Doxorubicin 25mg/m^2 IV push + bleomycin 10units/m^2 IV push + vinblastine 6mg/m2 IV over 5–10 minutes + dacarbazine 375mg/m^2 IV over 60 minutes. Repeat cycle every 4 weeks for 2 cycles followed by 4 cycles of ABVD or 4 cycles of escalated BEACOPP, cycles with or without subsequent radiation.
Doxorubicin + Vinblastine + Mechlorethamine + Etoposide + Vincristine + Bleomycin + Prednisone (Stanford V)	**Days 1 and 15**: Doxorubicin 25mg/m^2 IV push + vinblastine 6mg/m^2 IV over 5–10 minutes **Day 1**: Mechlorethamine 6mg/m^2 IV push **Days 8 and 22**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5–10 minutes + bleomycin 5units/m^2 IV push **Days 15 and 16**: Etoposide 60mg/m^2 IV over 60 minutes **Days 1–28**: Prednisone 40mg/m^2 orally every other day. Taper prednisone dose by 10mg every other day beginning Day 15 of Cycle 3. Repeat cycle every 4 weeks for 3 cycles with or without subsequent radiation therapy.

Bleomycin + Etoposide + Doxorubicin + Cyclophosphamide + Vincristine + Procarbazine + Prednisone (Escalated BEACOPP)	**Day 1**: Cyclophosphamide 1,250mg/m^2 IV over 60 minutes + doxorubicin 35mg/m2 IV push **Days 1–3**: Etoposide 200mg/m^2 IV over 2 hours **Days 1–7**: Procarbazine 100mg/m^2 orally daily. **Day 8**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5–10 minutes + bleomycin 10units/m^2 IV push. **Days 1–14**: Prednisone 40mg/m^2 orally daily. Repeat cycle in selected patients (IPS≥4, aged <60 years) every 3 weeks for 6 cycles or for 2 cycles followed by 4 cycles of ABVD in patients with a negative interim PET, with or without subsequent radiation therapy.

Second-Line Therapy

Regimen:	**Dosing:**
Brentuximab vedotin	**Day 1**: Brentuximab 1.8mg/kg (maximum 180mg) IV over 30 minutes; For patients with hepatic impairment: 1.2mg/kg (up to 120mg). Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.
Cyclophosphamide + Vincristine + Procarbazine + Prednisone (C-MOPP) (Category 2B)	**Day 1**: Cyclophosphamide 650mg/m^2 IV over 30 minutes + vincristine 1.4mg/m^2 (maximum 2mg) IV **Days 1–7**: Procarbazine 100mg/m^2 orally daily **Days 1–14**: Prednisone 40mg/m^2 orally daily. Repeat cycle every 4 weeks for 4–8 cycles. **OR** **Days 1 and 8**: Cyclophosphamide 500mg/m^2 IV over 30 minutes + vincristine 1.4mg/m^2 (maximum 2mg) IV over 5–10 minutes **Days 1–14**: Procarbazine 100mg/m^2 orally daily. **Days 1–3 and 8–10**: Prednisone 40mg/m^2 orally daily. Repeat cycle every 4 weeks for 4–8 cycles.
Dexamethasone + Cytarabine + Cisplatin (DHAP)	**Days 1–4**: Dexamethasone 40mg orally or IV daily **Day 1**: Cisplatin 100mg/m^2 IV continuous infusion over 24 hours **Day 2**: Cytarabine 2,000mg/m^2 IV over 3 hours every 12 hours. Repeat cycle every 3 to 4 weeks for 2–4 cycles (transplant candidates) or 4–8 cycles (non-transplant candidates).
Etoposide + Methylprednisolone + Cytarabine + Cisplatin (ESHAP)	**Days 1–4**: Etoposide 40mg/m^2 IV over 60 minutes + Methylprednisolone 500mg IV over 15 minutes + cisplatin 25mg/m^2 continuous IV infusion over 24 hours **Day 5**: Cytarabine 2,000mg/m^2 IV over 3 hours. Repeat cycle every 3–4 weeks for 2–4 cycles (transplant candidates) or 4–8 cycles (non-transplant candidates).
Everolimus	Everolimus 10mg PO daily until disease progression or unacceptable toxicity.
Gemcitabine + Carboplatin + Dexamethasone (GCD)	**Days 1 and 8**: Gemcitabine 1000mg/m^2 IV over 30 minutes **Day 1**: Carboplatin AUC 5mg • min/mL (maximum 800mg) IV over 60 minutes **Days 1–4**: Dexamethasone 40mg orally daily. Repeat cycle every 3 weeks for 2–4 cycles (transplant candidates) or 4–8 cycles (non-transplant candidates).
Gemcitabine + Vinorelbine + Pegylated liposomal doxorubicin (GVD)	<u>For transplant-naive patients</u>: **Days 1 and 8**: Gemcitabine 1,000mg/m^2 IV over 30 minutes + vinorelbine 20mg/m^2 IV over 5–10 minutes + pegylated liposomal doxorubicin 15mg/m^2 IV over 60 minutes. Repeat cycle every 3 weeks for 2–4 cycles (transplant candidates) or 4–8 cycles (nontransplant candidates). <u>For post-transplant patients</u>: Days 1 and 8: Gemcitabine 800mg/m^2 IV over 30 minutes + vinorelbine 15mg/m^2 IV over 5–10 minutes + pegylated liposomal doxorubicin 10mg/m^2 IV over 60 minutes. Repeat cycle every 3 weeks for 2–4 cycles (transplant candidates) or 4–8 cycles (non-transplant candidates).

Ifosfamide + Carboplatin + Etoposide (ICE)	**Days 1–3**: Etoposide 100mg/m^2 IV over 60 minutes **Day 2**: Carboplatin AUC 5mg • min/mL (max 800mg) IV + ifosfamide 5,000mg/m^2 IV + mesna 5,000mg/m^2 IV administered concurrently as a continuous infusion over 24 hours. Repeat cycle every 2–3 weeks for 2–4 cycles (transplant candidates) or 4–8 cycles (nontransplant candidates).
Ifosfamide + Gemcitabine + Vinorelbine (IGEV)	**Days 1–4**: Ifosfamide 200mg/m^2 IV over 2 hours plus mesna 2,600mg/m2 IV **Days 1 and 4**: Gemcitabine 800mg/m^2 IV over 30 minutes **Day 1**: Vinorelbine 20mg/m^2 IV over 5–10 minutes **Days 1–4**: Prednisone 100mg PO daily. Repeat cycle every 3 weeks for 2–4 cycles (transplant candidates) or 4–8 cycles (non-transplant candidates).
Carmustine + Cytarabine + Etoposide + Melphalan (Mini-BEAM)	**Day 1**: Carmustine 60mg/m^2 IV over 2 hours **Days 2–5**: Etoposide 75mg/m^2 IV over 60 minutes daily + cytarabine 100mg/m^2 IV over 3 hours every 12 hours **Day 6**: Melphalan 30mg/m^2 IV over 15 minutes. Repeat cycle every 4–6 weeks for 2–4 cycles.
Mitoxantrone + Ifosfamide + Mesna + Etoposide (MINE)	**Days 1–3**: Mesna 1.33 g/m^2 IV daily, and 500 mg PO daily 4 hours after each IV dose plus ifosfamide 1.33 g/m^2 IV daily, given concurrently with mesna, for 3 days. **Day 1**: Mitoxantrone 8mg/m^2 IV over 30 minutes. Repeat cycle every 3 weeks for 2–4 cycles (transplant candidates) or 4–8 cycles (non-transplant candidates).
Bendamustine	**Days 1 and 2**: Bendamustine 70–120mg/m^2 IV over 30 minutes. Repeat cycle every 4 weeks until maximal response or unacceptable toxicity.
Lenalidomide	**Days 1–21**: Lenalidomide 25mg orally daily. Repeat cycle every 4 weeks until disease progression or unacceptable toxicity.
MAINTENANCE THERAPY Brentuximab vedotin	**Day 1**: Brentuximab 1.8mg/kg (maximum 180mg) IV over 30 minutes.Repeat cycle ewvery 3 weeks until disease progression or unacceptable toxicity for a maximum of 1 year after HDT/SCR (if primary refractory disease or relapse occurred <12 months after primary therapy).

(Cancer Therapy Advisor).

Expectations (Prognosis) for Hodgkin's Lymphoma

Hodgkin's lymphoma is considered one of the most curable forms of cancer, especially if it is diagnosed and treated early. Unlike other cancers, Hodgkin's lymphoma is often very curable, even in its late stages.

With the right treatment, more than 90% of people with stage I or II Hodgkin's lymphoma survive for at least 10 years. If the disease has spread, the treatment may be more intense. However, 90% of people with advanced disease survive for at least 5 years.

Patients who survive 15 years after treatment are more likely to later die from other causes, including complications of the treatment, rather than from Hodgkin's disease.

People with Hodgkin's lymphoma whose disease returns within a year after treatment or who do not respond to the first treatment have a poorer outlook.

Patients will need to have regular examinations and imaging tests for years after treatment. This helps the doctor check for signs of the cancer returning, and for any long-term treatment effects.

Complications of Hodgkin's Lymphoma
Treatments for Hodgkin's lymphoma can have complications. Long-term complications of chemotherapy or radiation therapy include:

- Bone marrow diseases (such as leukaemia)
- Heart disease
- Inability to have children (infertility)
- Lung problems
- Other cancers
- Thyroid problems

Chemotherapy can cause low blood cell counts, which can lead to an increased risk of bleeding, infection, and anaemia. To reduce bleeding, apply ice and pressure. Use a soft toothbrush and electric razor for personal hygiene.

Always take an infection seriously during cancer treatments. Contact the treating doctor right away if fever develops or other signs of infection, especially if the white blood cell counts are low due to treatment. Planning rest periods during daily activities may help prevent fatigue due to anaemia (Cancer Research UK; Mayo Clinic; PubMed Health).

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, 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.
- 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 (CANSA) 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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