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

Fact Sheet
On
Burkitt 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]

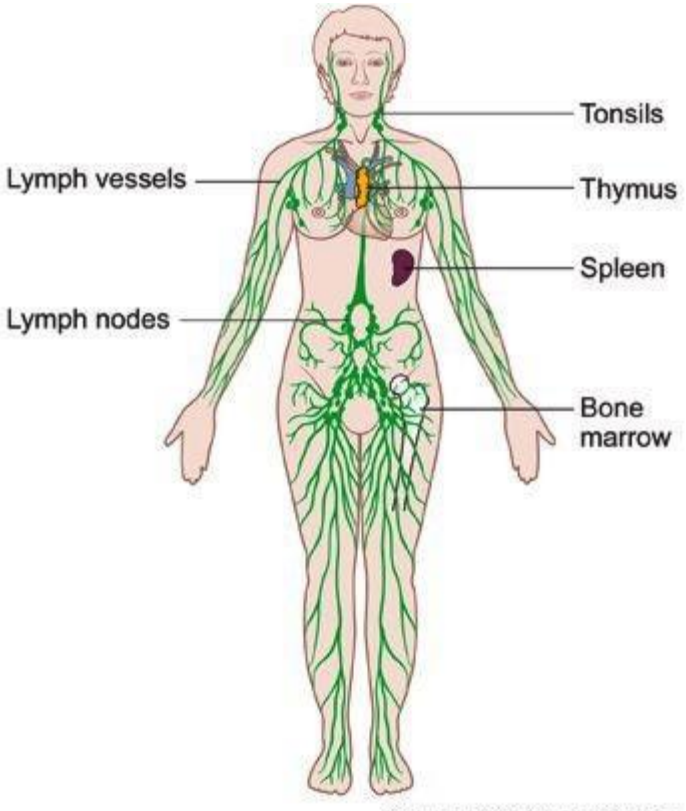
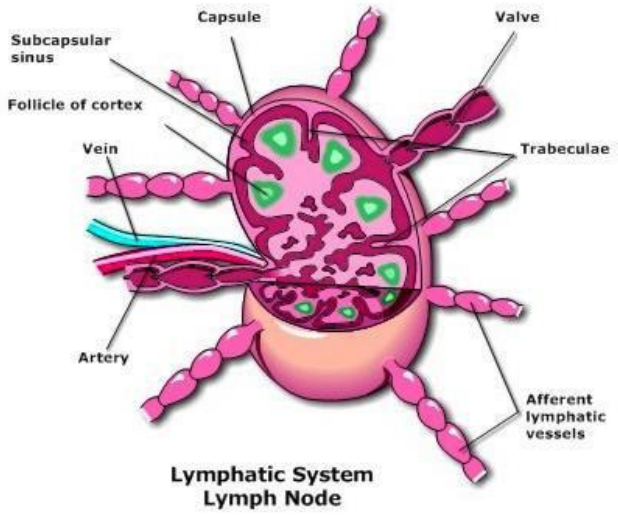


Diagram of the lymphatic system
Copyright © CancerHelp UK

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 didn't drain the excess fluid from the tissues, 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, 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)

**Burkitt Lymphoma**

Burkitt lymphoma is a very fast growing form of non-Hodgkin's lymphoma and for this reason it is often discussed separately from the other forms of non-Hodgkin's Lymphomas.

Alternative names include: B-cell lymphoma; High-grade B-cell lymphoma. Outside of Africa, Burkitt lymphoma is rare.

Burkitt lymphoma is named after British surgeon Denis Burkitt, who first identified this unusual disease in 1956 among children in Africa. In Africa, Burkitt lymphoma is common in young children who also have malaria and Epstein-Barr, the virus that causes infectious mononucleosis. It's thought that malaria may weaken the immune system's response to

Epstein-Barr, allowing it to change infected B-cells into cancerous cells. About 98% of African cases are associated with Epstein-Barr infection.

**Causes, Incidence, and Risk Factors of Burkitt Lymphoma**

Burkitt Lymphoma (BL) was first discovered in children in certain parts of Africa, but it now also occurs in other parts of the world. Burkitt Lymphoma is named after the doctor who first described this kind of tumour in children in Africa. This type of Burkitt Lymphoma is known as endemic or African-type Burkitt Lymphoma. It also occurs in people in other countries and this is usually called sporadic Burkitt Lymphoma. The African type of Burkitt Lymphoma is a rare type of B-cell lymphoma and is closely associated with the Epstein-Barr virus (EBV), the main cause of infectious mononucleosis. It affects both children and young adults. People with HIV have an increased risk for this condition. The North American form of Burkitt Lymphoma is not linked to EBV.

Butkitt Lymphoma can also affect people who have poor immunity.

The different types are:

- *Endemic BL* - This is found in central Africa, usually in children, and is strongly linked to reduced resistance to a common virus called the Epstein-Barr virus (EBV). The jaw bone is often affected, which is rare in other types of BL.

- *Sporadic BL* - This is also linked with the Epstein-Barr virus, which causes glandular fever, but less clearly than with endemic BL. Epstein-Barr is a common virus and it is not known why it may increase the risk of lymphoma in some people but not others.

- *Immunodeficiency-associated BL* - This usually occurs in people with HIV or AIDS, who have poor immunity, or in people who are taking medicines (immunosuppressive drugs) after an organ transplant.

- *Non-Burkitt Lymphoma* - There is also a type of small, non-cleaved lymphoma that has a somewhat different appearance under the microscope that is called non-Burkitt's lymphoma, which usually occurs in adults.

**Incidence of Burkitt Lymphoma in South Africa**

According to the National Cancer Registry (2012) the following number of Burkitt Lymphoma cases were histologically diagnosed in South Africa during 2012:

| Group - Males 2012 | Actual No of Cases | Estimated Lifetime Risk | Percentage of All Cancers |
|---|---|---|---|
| All males | 107 | 1:3 013 | 0,29% |
| Asian males | 3 | 1:3 016 | 0,38% |
| Black males | 80 | 1:3 075 | 0,69% |
| Coloured males | 11 | 1:3 016 | 0,25% |
| White males | 13 | 1:2 337 | 0,06% |

| Group - Females 2012 | Actual No of Cases | Estimated Lifetime Risk | Percentage of All Cancers |
|---|---|---|---|
| All females | 63 | 1:5 279 | 0,17% |
| Asian females | 1 | 1:8 814 | 0,10% |
| Black females | 53 | 1:5 086 | 0,32% |
| Coloured females | 3 | 1:7 705 | 0,08% |
| White females | 6 | 1:4 719 | 0,04% |

The frequency of histologically diagnosed cases of Burkitt Lymphoma in South Africa for 2012 was as follows (National Cancer Registry, 2012):

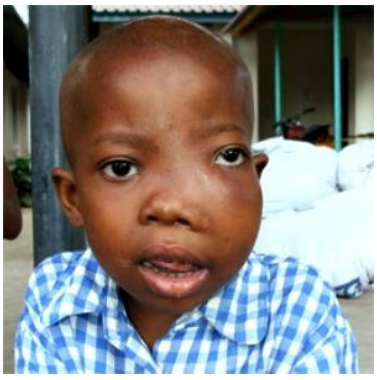
| Group - Males 2012 | 0 – 19 Years | 20 – 29 Years | 30 – 39 Years | 40 – 49 Years | 50 – 59 Years | 60 – 69 Years | 70 – 79 Years | 80+ Years |
|---|---|---|---|---|---|---|---|---|
| All males | 28 | 10 | 25 | 22 | 15 | 3 | 1 | 1 |
| Asian males | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Black males | 17 | 6 | 23 | 13 | 11 | 2 | 1 | 1 |
| Coloured males | 3 | 3 | 0 | 3 | 1 | 0 | 0 | 0 |
| White males | 5 | 1 | 1 | 1 | 4 | 3 | 0 | 0 |

| Group - Females 2012 | 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 | 12 | 5 | 19 | 20 | 4 | 3 | 0 | 0 |
| Asian females | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Black females | 9 | 5 | 16 | 15 | 4 | 1 | 0 | 0 |
| Coloured females | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 |
| White females | 2 | 0 | 1 | 2 | 0 | 1 | 0 | 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.

**Symptoms of Burkitt Lymphoma**

Burkitt lymphoma may first be noticed as a swelling of the lymph nodes (glands) in the neck, groin, or under the arm. These swollen lymph nodes are often painless, but can grow very rapidly. The disease can also start in the ovaries, testes, brain, and spinal fluid.



[Picture Credit: Burkitt Lymphoma]

Symptoms include:

- Fever
- Night sweats
- Unexplained swollen lymph nodes
- Unexplained weight loss

**Tests for Burkitt Lymphoma**

Tests used in the diagnosis of Burkitt Lymphoma include:

- Bone marrow biopsy

- Chest x-ray
- CT scan of the chest, abdomen, and pelvis
- Complete blood count (CBC)
- Examination of the spinal fluid
- Lymph node biopsy
- PET scan

**Diagnosis of Burkitt Lymphoma**

Minimal diagnostic criteria to qualify for the diagnosis of BL, the following must be fulfilled:

- Presence of B cell markers in tumour (CD20 and/or CD79)
- 95% or higher MKI67 expression
- Cytogenetic or FISH evidence of t(8;14)(q24;32), or t(14;18)(q32;q21) and 3q27 affecting the c-myc gene

Other Useful Diagnostic Information:

- Absence of BCL-2 and abnormal TP53 expression
- A peripheral phenotyepe, e.g. absence of CD34 and TdT expression on flowcytometry

Diagnostic Tests Required Before Commencing Treatment include:

- HIV test
- Hepatitis B & C status
- Electrocardiogram (ECG)
- Echocardiogram or MUGA scan as per local protocol for assessment of cardiac function (A MUGA scan (Multi Gated Acquisition Scan) is a time-proven nuclear medicine test designed to evaluate the function of the right and left ventricles of the heart, thus allowing informed diagnostic intervention in heart failure. It is also called radionuclide angiography, or gated blood pool imaging, as well as SYMA (Synchronised Multigated Acquisition) scan. This modality uniquely provides a cine image of the beating heart, and allows the interpreter to determine the efficiency of the individual heart valves and chambers. MUGA/Cine scanning represents a robust adjunct to the now more common echocardiogram).
- U & E (blood urea and electrolyte)
- LFT (liver function test)
- Bone scan
- Creatinine Clearance
- LDH (lactate dehydrogenase test)
- Urate
- Staging CT scan
- MRI Brain and spinal cord

**Staging of Burkitt Lymphoma**
The stage of non-Hodgkin lymphoma describes how many groups of lymph nodes are affected, where they are in the body and whether other organs such as the bone marrow or liver are involved. The system that's usually used for BL is the St Jude/Arbor staging system. Nodal means that the lymphoma is in the lymph nodes. Sometimes the lymphoma can start in areas outside the lymph nodes. This is called extranodal lymphoma.

*Stage 1*
There is one extranodal tumour or a single group of lymph nodes affected, but not in the chest or abdomen. A group of lymph nodes refers to lymph nodes in one area of the body, such as in the armpit, on one side of the neck or in the groin.

*Stage 2*
Can be any of the following:

- There is one extranodal tumour and nearby lymph nodes are affected.
- There are two extranodal tumours on the same side of the diaphragm (the sheet of muscle under the lungs), with or without nearby lymph nodes affected. The lymphoma started in the stomach or bowel – nearby nodes may or may not be affected.
- The lymphoma is in two or more areas of lymph nodes on the same side of the diaphragm.

*Stage 2R*
The lymphoma was in the abdominal area but has been completely removed by surgery.

*Stage 3*
Can be any of the following:
There are two extranodal tumours on opposite sides of the diaphragm.

- The lymphoma started in the lungs, chest area or thymus gland.
- The lymphoma is affecting the area within or around the spinal cord.
- The lymphoma started in the abdomen and affects a large area.
- Two or more nodal areas are affected on opposite sides of the diaphragm.

*Stage 3A*
The lymphoma is in the abdominal area only and cannot be removed by surgery.

*Stage 3B*
The lymphoma is affecting several organs within the abdomen.

*Stage 4*
Any of the above and at diagnosis, the brain and spinal cord (central nervous system) and/or the bone marrow are also affected.

**Grading of Burkitt Lymphoma**
For practical purposes, non-Hodgkin lymphomas are divided into two groups: low-grade and high-grade. Low-grade lymphomas are usually slow-growing and high-grade lymphomas

grow more quickly. Burkitt Lymphoma is a high-grade lymphoma. This means that it grows quickly and needs to be treated immediately with chemotherapy.

**Treatment of Burkitt Lymphoma**

Chemotherapy is used to treat this type of cancer. Commonly used medicines include:

- Prednisone
- Cyclophosphamide
- Ifosfamide
- Vincristine
- Cytarabine
- Doxorubicin
- Methotrexate, and
- Etoposide.

Intensive systemic chemotherapy is the treatment of choice for this aggressive disease in all its stages. All clinical variants of Burkitt lymphoma are treated generally the same. The overall survival rate associated with Burkitt lymphoma depends upon the stage of the disease at initial diagnosis. Patients with localised disease respond well to chemotherapy and have an excellent survival rate. Patients with disseminated disease respond less well to chemotherapy and have a less favourable survival rate. Increasing age has also been associated with inferior outcome in most clinical trials.

For patients who refuse, or are not candidates for clinical trials, short-duration, intensive, alkylator-based, multi-agent chemotherapy regimens with adequate central nervous system (CNS) prophylaxis are necessary. Administration of less intensive chemotherapy regimens used in other non-Hodgkin lymphomas (NHL) (e.g., CHOP [cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine and prednisone]) usually results in frequent relapses and inferior survival. Of particular importance is the rapid administration of successive cycles of intensive multidrug therapy to prevent tumour regrowth. Dose reduction should also be avoided if possible.

Most adult Burkitt lymphoma regimens were initially adopted from the paediatric study protocols that used several known active agents, including cyclophosphamide, vincristine, methotrexate, doxorubicin, and cytarabine. The French (LMB 81, 84, 86, and 89) and the German (B-NHL 83, B-NHL 86) protocols as well as the CODOX-M/IVAC regimen (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate / ifosfamide, etoposide, high-dose cytarabine) were modified and used in adult patients with acceptable outcomes (2-year overall survival: 40-74%). Other protocols (hyper-CVAD [modified fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone], Cancer and Leukaemia Group B [CALGB] 9251, etc) were evaluated primarily in adults.

A study by Todeschini, *et al* found that intensive paediatric-based chemotherapy regimen increased remission and survival rates in both children and adults with Burtkitt lymphoma.

Even though a standard regimen is not available yet, in general, three treatment approaches are available:

- Intensive, short-duration regimens like CODOX-M/IVAC (Magrath regimen) and the CALGB 9251 protocol

- Long-duration chemotherapy similar to acute lymphoblastic leukaemia (ALL) treatment, like hyper-CVAD and the CALGB 8811 protocol
- Combination regimens followed by autologous stem cell transplantation (SCT)
- Most current regimens have added rituximab to previously established chemotherapy regimens

Despite the fact that no direct comparison has been done among these different approaches, the short-duration, more intense regimens are usually preferred, because they are faster to administer (ALL-type treatment may take up to 2y and usually involves a maintenance arm) and less complicated than ALL-type treatment or SCT. The regimen most frequently used is CODOX-M/IVAC.

Each of the above mentioned regimens carries a 60-70% chance of prolonged progression-free and overall survival, but that is unfortunately associated with a significant toxicity profile. No toxic deaths were reported in the initial study by Magrath (CODOX-M/IVAC), but the rate of grade ¾ neutropenia was 100%; thrombocytopenia, 96%; mucositis, 61%; and sepsis, 22%. Similar toxicities were seen on the CALGB 9251 protocol.
(MedScape)

**Expectations (Prognosis) of Burkitt Lymphoma**
More than half of those with Burkitt lymphoma can be cured with intensive chemotherapy. The cure rate may be lower if the cancer spreads to the bone marrow or spinal fluid. The outlook is poor if the cancer comes back after a remission.

**Complications of Burkitt Lymphoma**
- Complications of treatment (radiation therapy or chemotherapy)
- Spread of the cancer

(PubMed; MacMillan Cancer Support; Medline Plus; WebMD; Boston Children's Hospital; The Burkitt's Lymphoma Society; Merseyside & Cheshire Cancer Network)

**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.

<u>Types of Clinical Trials</u>
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.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

**Sources and References**


**American Cancer Society**
http://www.cancer.org/Cancer/Non-HodgkinLymphoma/DetailedGuide/non-hodgkin-lymphoma-risk-factors

**Autologous Transplant**
http://multiple-sclerosis-research.blogspot.com/p/grand-challenges-in-ms.html

**Boston Children's Hospital**
http://childrenshospital.org/az/Site2182/mainpageS2182P1.html

**Cancer Research UK**
http://www.cancerresearchuk.org/cancer-info/cancerstats/types/hodgkinslymphoma/riskfactors/hodgkins-lymphoma-risk-factors#genetics

**Cells of the Immune System**
http://www.alohamedicinals.com/how-your-immune-system-works.html#.VBvpG_mSySo

**eMedicineHealth**. Lymphoma. http://www.emedicinehealth.com/lymphoma/article_em.htm

**Hodgkin's Lymphoma**
https://www.google.co.za/search?q=hodgkin%27s+lymphoma&source=lnms&tbm=isch&sa=X&ei=Kl-ZU_bUJaev7Ab_q4CwCA&sqi=2&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=wrUKxr_raB8ehM%3A%3B3MTF6fAZjSVlEM%3BwrUKxr_raB8ehM%3A&imgrc=wrUKxr_raB8ehM%253A%3ByWB-1qzXMW4rDM%3Bhttp%253A%252F%252Fs2.hubimg.com%252Fu%252F6438913_f260.jpg%3Bhttp%253A%252F%252Fkimhdimino.blogspot.com%252F2013%252F03%252Fhodgkins-disease-overview.html%3B260%3B195

**KidsHealth.** The Lymphatic System.
http://kidshealth.org/parent/general/body_basics/spleen_lymphatic.html

**Lymphatic System**
http://www.google.co.za/imgres?start=83&hl=en&sa=X&rlz=1T4LENN_enZA490ZA490&biw=1366&bih=613&tbm=isch&prmd=imvns&tbnid=-fIgwTmsqqhLNM:&imgrefurl=http://cancerhelp.cancerresearchuk.org/type/hodgkins-lymphoma/about/what-is-hodgkins-lymphoma&docid=sUkIP6oPMYIj-M&imgurl=http://cancerhelp.cancerresearchuk.org/prod_consump/groups/cr_common/%2540cah/%2540gen/documents/image/crukmig_1000img-12066.jpg&w=350&h=431&ei=YdRSUOCpMOSx0QXWr4DABQ&zoom=1&iact=hc&vpx=1106&vpy=249&dur=2671&hovh=249&hovw=202&tx=127&ty=114&sig=107310304455409594391&page=4&tbnh=129&tbnw=105&ndsp=30&ved=1t:429,r:29,s:83,i:96]

**Lymph Node**
http://www.google.co.za/imgres?hl=en&sa=X&rlz=1T4LENN_enZA490ZA490&biw=1366&bih=613&tbm=isch&prmd=imvns&tbnid=y5UPisMY6d3v2M:&imgrefurl=http://www.smartdraw.com/examples/view/non-hodgkin%2Blymphoma%2B-%2Bcell/&docid=r4nBtXE1dXFreM&imgurl=http://wc1.smartdraw.com/examples/content/Examples/10_Healthcare/Cancer_Illustrations/Non-Hodgkin_Lymphoma_-_Cell_L.jpg&w=842&h=627&ei=RNRSUM_6O9DY0QX1vYDABQ&zoom=1&iact=rc&dur=52

7&sig=107310304455409594391&page=2&tbnh=131&tbnw=175&start=23&ndsp=29&ved=1t:429,r:19,s:23,i:206&tx=110&ty=82]

**Lymphoma Association UK**
http://www.lymphomas.org.uk/sites/default/files/pdfs/Angioimmunoblastic-T-cell-lymphoma.pdf

**Lymphomainfo.net**
http://www.lymphomainfo.net/nhl/classify.html
http://www.lymphomainfo.net/nhl/types/t-ail.html

**Lymphoma Research Foundation**
http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6300145

**MacMillan Cancer support**
http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Lymphomanon-Hodgkin/TypesofNHL/Burkitt.aspx

**Medscape**
http://emedicine.medscape.com/article/1099386-overview#aw2aab6b4

**Merseyside & Cheshire Cancer Network**
http://www.mccn.nhs.uk/userfiles/documents/Guidelines%20for%20treatment%20of%20Burkitts%20Lymphoma%20DEC%202010.pdf

**Mayo Clinic**
http://www.mayoclinic.com/health/hodgkins-disease/DS00186/DSECTION=risk-factors

**Medline Plus**
http://www.nlm.nih.gov/medlineplus/ency/article/001308.htm

**MedScape**
http://emedicine.medscape.com/article/1447602-treatment#d9

**National Cancer Institute**
http://www.training.seer.cancer.gov/lymphoma/abstract-code-stage/
http://www.cancer.gov/clinicaltrials/learningabout/what-are-clinical-trials

**Non-Hodgkin's Lymphoma**
https://www.google.co.za/search?q=non-hodgkin%27s+lymphoma&source=lnms&tbm=isch&sa=X&ei=AGCZU8q1KsLD7Aax9IH4Aw&sqi=2&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=kKB9P4GyA_Fu3M%3A%3B2h1pJ-GD7YW-PM%3BkKB9P4GyA_Fu3M%3A&imgrc=kKB9P4GyA_Fu3M%253A%3BNDhAy5EHR6ijXM%3Bhttp%253A%252F%252Fwww.cixip.com%252FPublic%252Fkindeditor%252Fattached%252Fimage%252F20120925%252F20120925100954_31690.jpg%3Bhttp%253A%252F%252Fwww.cixip.com%252Findex.php%252Fpage%252Fcontent%252Fid%252F613%3B537%3B600

**PubMed Health. Hodgkin's Lymphoma**.
http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001606/
http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001607/
http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002285/

**Rodriguez-Justo, M., Attygalle, A.D., Munson, P., Roncador, G, Maragioti, T. & Pirisw, M.A.** 2009. Antioimmunoblastic T-Cell lymphoma with hyperplastic germinal centres: a neoplasia with origin in the outer zone of the germinal centre? Clinicopathological and immunohistochemical study of 10 cases with follicular T-cell markers. *Modern Pathology*, 22:753-761. doi:10.1038/modpathol.2009.12; published online 27 March 2009

**The Burkitt's Lymphoma Society**
http://burkittslymphomasociety.com/

**The Immune System**
http://www.humanvitaminhealth.com/yourimmunesystem.html

**University of Maryland Medical Center**
http://www.umm.edu/patiented/articles/what_risk_factors_non-hodgkins_lymphomas_000084_2.htm

**WebMD**
http://www.webmd.com/cancer/burkitt-lymphoma-prognosis-diagnosis-treatments