Cancer Association of South Africa (CANSA)

Research • Educate • Support

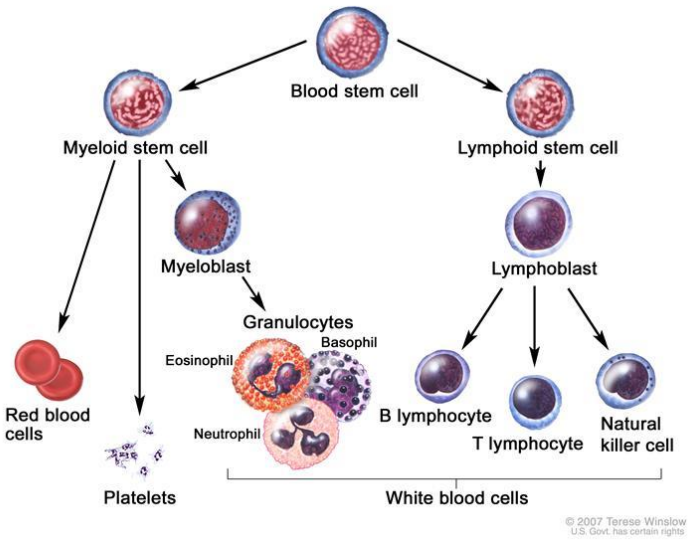
Fact Sheet on Adult Chronic Lymphoblastic Leukaemia (CLL)

Introduction

The word *leukaemia* can literally be translated to mean 'white blood' and is used to describe a variety of cancers that begin in the blood-forming cells (lymphocytes) of the bone marrow.

Leukaemias are divided into two major types:

- Acute Leukaemia which progresses quickly with many immature white cells
- Chronic Leukaemia which progresses more slowly and has more mature white cells



[Picture Credit: Blood Cell Development]

Both leukaemia and lymphomas (Hodgkin's disease and non-Hodgkin's lymphomas) are cancers of lymphocytes. The difference is that leukaemia starts in the bone marrow while lymphomas originate in lymph nodes and then spread to the bone marrow or other organs.

White blood cells (*leukocytes*) evolve from immature cells referred to as *blasts*. Malignancy of these blast cells is the source of leukaemias, which generally progress as follows:

- Normally, blasts constitute 5% or less of healthy bone marrow. In leukaemia, however, these blasts remain immature and multiply continuously but fail to mature properly, eventually constituting between 30 - 100% of the bone marrow.
- In time, these malignant blast cells fill up the bone marrow and prevent production of healthy red cells, platelets and mature white cells (leukocytes).
- Malignant blasts spill out of the marrow into the bloodstream and lymph system and can travel to the brain and spinal cord (the central nervous system). Some blasts are

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called *lymphoblasts* (which normally become mature cells called *lymphocytes*) and others are called *myeloblasts* (which mature to *myeloid* cells).
(University of Maryland Medical Center).

Chronic Lymphoblastic Leukaemia

Chronic lymphoblastic leukaemia (CLL) is a type of slow growing leukaemia that affects developing *B-lymphocytes* (also known as B-cells).These cells are specialised white blood cells. Under normal conditions they produce immunoglobulins (also called antibodies) that help protect individuals against infection and disease. In people with CLL, lymphocytes undergo a malignant (cancerous) change and become leukaemic cells.

For many people, CLL remains stable for many months and years and has little, if any impact on their lifestyle or general health. Around 30% of people diagnosed with CLL never require any treatment for their disease and can survive for many years despite their diagnosis. For others, the leukaemic cells multiply in an uncontrolled way. These cells are abnormal and as such they are unable to function properly.

The leukaemic cells live longer than they should and accumulate in the bone marrow, blood stream, lymph nodes (glands), spleen, liver and other parts of the body. Over time, an excess number of lymphocytes crowd the bone marrow, and interfere with normal blood cell production.

The bone marrow produces inadequate numbers of red cells, normal white blood cells and platelets. This leads to some people with CLL being more susceptible to anaemia, recurrent infections and bruising and bleeding easily. Circulating red blood cells and platelets can also be damaged by abnormal proteins made by the leukaemic cells.
(Leukaemia Foundation).

Incidence of Adult Chronic Lymphoblastic Leukaemia in South Africa

In providing the incidence figures of Leukaemia in South Africa, The National Cancer Registry (2012) does not make provision for the reporting of the different types of Leukaemia – it also does not differentiate between acute and chronic Leukaemia - neither does it provide for different statistics for cases of adult and childhood Leukaemia.

According to the National Cancer Registry (2013) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2013:

Group - Males 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	351	1:645	1,98%
Asian males	8	1:907	1,00%
Black males	184	1:1 081	1,71%
Coloured males	46	1:441	1,10%
White males	114	1:282	0,56%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	279	1:1 068	0,76%
Asian females	6	1:1 625	0,60%
Black females	141	1:1 695	0,90%
Coloured females	42	1:722	1,03%
White females	91	1:394	0,57%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2013 was 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	103	28	24	42	42	51	39	12
Asian males	3	1	1	0	1	2	0	0
Black males	65	19	15	28	18	15	10	1
Coloured males	14	3	2	4	6	8	4	1
White males	12	5	6	18	18	23	30	11

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	55	34	28	30	45	35	29	16
Asian females	3	0	0	1	0	1	0	1
Black females	28	26	21	13	16	14	7	4
Coloured females	5	4	3	9	10	4	2	2
White females	14	3	4	7	18	13	20	8

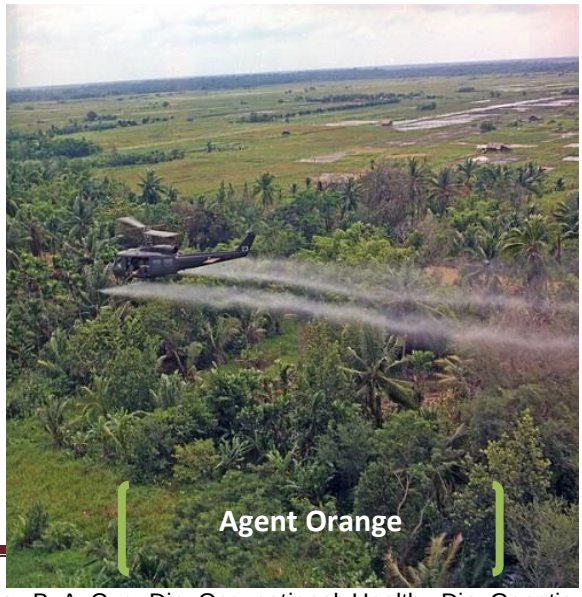
N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Risk Factors for Adult Chronic Lymphoblastic Leukaemia

A risk factor is something that affects a person's chance of getting a disease like cancer. For example, exposing skin to strong sunlight is a risk factor for skin cancer. Smoking is a risk factor for a number of cancers. Having a risk factor, or even several risk factors, does not mean that someone will get the disease. Many people who get the disease may not have had any known risk factors. Even if a person has a risk factor and develops cancer, it is often very difficult to know how much that risk factor contributed to the cancer.

There are very few risk factors for adult chronic lymphoblastic leukaemia (CLL).

Certain chemical exposures – some studies have linked exposure to Agent Orange, a herbicide used during the Vietnam War, to an increased risk for CLL. Some other studies have suggested that faming and long-term exposure to some pesticides may be linked to an increased risk for CLL, but more research is needed.



[Picture Credit: Agent Orange]

Family history – first-degree relatives (parents, siblings or children) of CLL patients have more than twice the risk for Adult Chronic Lymphoblastic Leukaemia. A family history of CLL or cancer of the lymph system. Having relatives who are Russian, Jewish or Eastern European Jewish increases one's risk.

Sex – CLL is slightly more common in males than females. The reasons for this are not known.

Gene mutations – scientists know that most cases of leukaemia are associated with specific gene mutations, but in most cases, it is not clear what causes those mutations.

Age – it is largely a disease of older adults. Being middle-aged or older – the average age of diagnosis is 72 years.

A Second Cancer – If one has CLL he/she has a higher risk of developing a second cancer.

(American Cancer Society; Memorial Sloan Kettering Cancer Center; Genentech; American Cancer Institute; Leukaemia and Lymphoma Research; Web MD).

Signs and Symptoms of Adult Chronic Lymphoblastic Leukaemia
Usually CLL does not cause any symptoms and is found during a routine blood test. Sometimes symptoms occur that may be caused by CLL or by other conditions.

One should check with a doctor if any of the following problems are present:

- Painless swelling of the lymph nodes in the neck, underarm, stomach, or groin
- Feeling very tired
- Pain or fullness below the ribs
- Fever and infection
- Night sweats
- Bruising or bleeding easily
- Weight loss for no known reason
- An enlarged spleen
- Rapidly becoming more ill
- Fast heart beat and breathing

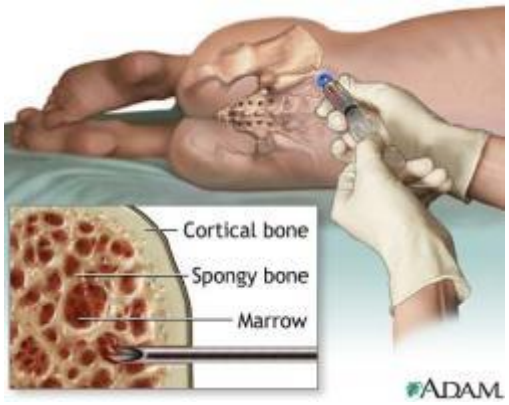
(American Cancer Institute; Leukaemia and Lymphoma research; Drugs.Com).

Diagnosis of Adult Chronic Lymphoblastic Leukaemia
The following tests may be used to diagnose CLL:

Blood tests: a complete blood count (CBC; a routine blood test) is the first test used to begin the process of diagnosing CLL. It is used to measure the number of different types of cells in a sample of a person's blood. A person may have CLL if the blood contains too many white blood cells (called a high white blood cell count). The doctor will also use the blood test to find out which types of white blood cells are increased.

Bone marrow aspiration and biopsy: CLL can usually be diagnosed with blood tests because the cancerous cells are easily found in the blood; therefore, a bone marrow biopsy and

aspiration is not needed for most patients. These two procedures are similar and often done at the same time before starting treatment.



[Picture Credit: Bone Marrow Aspiration]

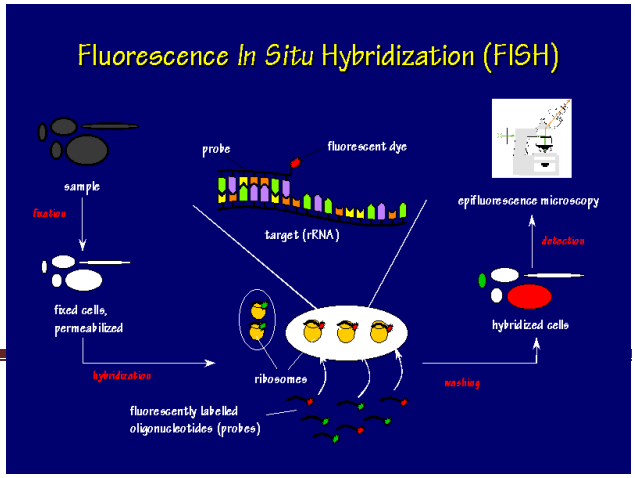
Bone marrow has both a solid and a liquid part. A bone marrow biopsy is the removal of a small amount of solid tissue using a needle. An aspiration removes a sample of fluid with a needle. The sample(s) are then analysed by a pathologist (a doctor who specialises in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease). A common site for a bone marrow biopsy and aspiration is the pelvic bone, which is located in the lower back by the hip. The skin in that area is usually numbed with medication beforehand, and other types of anaesthesia (medication to block the awareness of pain) may be used.

For some patients, a bone marrow aspiration and biopsy may be used to help determine prognosis (chance of recovery) or provide more information about the reasons that other blood counts may be abnormal. Although a bone marrow biopsy is usually not needed to diagnose CLL, it is often done before beginning treatment.

[Picture Credit: Flow Cytometry]

<u>Flow cytometry and cytochemistry</u>: in these tests, cancer cells are treated in the laboratory with chemicals or dyes that provide information about the leukaemia and its subtype. CLL cells have distinctive markers (cell surface proteins) on the outside of the cell. The pattern of these markers is called the immunophenotype. These tests are used to distinguish CLL from other kinds of leukaemia, which can also involve lymphocytes. Both tests can be done from a blood sample. Flow cytometry (also called immunophenotyping) is the most important test to confirm a diagnosis of CLL.

<u>Molecular testing</u>: the doctor may recommend running laboratory tests on the leukaemia cells to identify specific genes, proteins, chromosome changes, and other factors unique to the leukaemia. Because CLL cells divide very slowly, looking at the chromosomes often is less useful than using tests to find specific genetic mutations (changes).



[Picture Credit: FISH]

Fluorescence *in situ* hybridisation (FISH) assays detect a deletion of the long arm of chromosome 13 [del(13q)] in about half of patients.

Other common abnormalities include an extra copy of chromosome 12 (trisomy 12), del(11q) or del(17p). Results of these tests can determine how quickly the disease will progress and will help decide whether your treatment options include a type of treatment called targeted therapy.

Imaging tests: CLL is generally found in many parts of the body, even if the disease has been diagnosed early. Sometimes imaging tests may be recommended to find out the parts of the body affected by CLL or to find out whether particular symptoms may be related to CLL. Imaging tests may also be used to see how well treatment is working.

- An x-ray is a way to create a picture of the structures inside of the body, using a small amount of radiation. It may show if cancer is growing in lymph nodes in the chest.
- A computed tomography (CT or CAT) scan (a three-dimensional picture of the inside of the body) can detect lymph nodes with CLL around the heart, windpipe, lungs, and abdomen, and pelvis. A CT scan can also be used to measure the size of the lymph nodes. Sometimes, a contrast medium (a special dye) is injected into a patient's vein or given orally (by mouth) to provide better detail. CT scans can also determine if CLL is in other organs, such as the spleen.
- Positron emission tomography (PET) scans have not been proven to be helpful in diagnosing or staging CLL.

Imaging tests are rarely needed to diagnose CLL, but they are sometimes used before treatment to find all parts of the body that are affected by CLL.

After these diagnostic tests are done, the doctor will review all of the results. If the diagnosis is leukaemia, these results also help the doctor describe the disease; this is called staging. (Medscape; Cancer.Net).

Staging of Adult Chronic Lymphoblastic Leukaemia

Two systems for staging of CLL are in use. Both systems are based upon results of a physical examination and blood tests. Staging of CLL helps determine how likely it is that a patient will develop serious problems related to his/her illness. Patients at Rai Stage 0 are considered to be at low risk, those at stages I or II are at intermediate risk, and those at stage III or IV are at high risk.

The Rai System – the Rai system is based on an analysis of how the body is affected by the abnormal lymphocytes. There are five stages. The higher numbers indicate a more advanced stage of the disease.

Stage 0: increased numbers of abnormal lymphocytes are found in the blood or bone marrow. Lymph nodes/organs are not swollen. Production or red blood cells and platelets is normal.

Stage I: increased abnormal lymphocytes and enlarged lymph nodes.

Stage II: increased abnormal lymphocytes with enlarged liver or spleen, with or without enlarged lymph nodes.

Stage III: increased abnormal lymphocytes with anaemia (low red blood cell count), with or without an enlarged spleen, liver or lymph nodes.

Stage IV: increased abnormal lymphocytes with a low platelet count, with or without anaemia, enlarged liver, spleen or lymph nodes (Uptodate; Cancer Council Australia; Cleveland Clinic).

The Binet System – This system considers the five possible sites where lymphocytes can collect (lymph nodes in the neck, armpit and groin, and lymphocyte-containing channels in the spleen and liver, and also whether anaemia or low platelet counts are present. With this system patients have progressively increasing risk, with stage A as the lowest and stage C as the highest risk group. There are three stages:

Stage A: fewer than three involved sites
Stage B: three or more involved sites
Stage C: presence of anaemia or low platelet counts
(Uptodate; Cancer Research UK).

Treatment of Adult Chronic Lymphoblastic Leukaemia
Individuals who do not have symptoms of chronic lymphoblastic leukaemia are usually not treated for their disease. They should, however, be monitored regularly with blood tests and physical examination about every three months for at least the first year after diagnosis. This is done to determine how aggressive the disease is.

Treatment of localised adult CLL – individuals who have Stage I chronic lymphoblastic leukaemia are sometimes treated with radiation therapy. This refers to the exposure of tissues to high-energy X-rays in order to slow or stop their growth. Unlike normal cells, leukaemic cells cannot repair the damage caused by exposure to X-rays, particularly if it is administered over several days. This prevents the leukaemic cells from growing further and causes them to eventually die.

Treatment of advanced or symptomatic CLL – individuals with advanced or symptomatic CLL are generally treated first with chemotherapy. Chemotherapy refers to the use of medicines to stop or slow the growth of cancer cells. It works by interfering with the ability of rapidly growing cells (like cancer cells) to divide or multiply.

The administration of a chemotherapy drug or combination of drugs is referred to as a regimen. Regimens may be given in cycles. A cycle of chemotherapy refers to the time it takes to give th3e drugs and the time required for the body to recover. A typical chemotherapy regimen is at least a one-hour intravenous infusion of two or more different chemotherapy medications given once every three to four weeks. This three- or four-week period is one cycle of therapy.

One or more of the following chemotherapy drugs may be given:

Fludarabine: when used in combination regimens, can often induce partial or complete remission of CLL. The most common side effects are low blood counts and fever. Older

patients seem to be at higher risk of serious side effects from this medicine, including an increased risk of severe infections.

Rituximab: is a monoclonal antibody which means it is a purified protein that targets a specific group of cells, in this case cancer cells. It treats CLL by attacking specific substances (antigens) on the surface of the leukaemic cells. This type of treatment has advantages over other cancer treatments, which targets all rapidly multiplying cells.

Cyclophosphamide: is a chemotherapy drug that may be used in combination with other drugs in people with CLL. It can be given by mouth or through intravenous infusion. Side effects include low blood counts, nausea and vomiting, hair loss, and irritation of the bladder.

Alemtuzamab: is a monoclonal antibody used to treat CLL by attacking specific substances (antigens) on the surface of leukaemic cells. The antigens targete3d by this drug are different from those targeted by rituximab. It may not be available in all countries.

Bendamustine: may be given by itself or in combination with rituximab as an initial treatment for CLL, as well as in previously treated patients.

Obinutuzamab: is a monoclonal antibody that targets B lymphocytes. It is often used in combination with other drugs.

Treatment of relapsed CLL – if relapse occurs six or more months after treatment ends, it is often possible to successfully use the same chemotherapy regimen again or use another chemotherapy treatment.

Treatment of refractory (resistant) CLL – if a person's disease is refractory or relapses sooner than six months after treatment ends, the options for treatment are limited. Depending on the individual's situation, the following options should be discussed:

- Participation in a clinical trial
- Haematopoietic stem cell (bone marrow) transplantation\treatment with alternate chemotherapy regimens
- Treatment to reduce CLL-related symptoms and complications

Removal of the spleen (splenectomy) – a number of individuals with CLL will develop an enlarged spleen. While this often responds to treatment with chemotherapy or radiation, removal of the spleen is more likely to provide longer lasting benefits including increases in red blood cell and platelet counts.

Bone marrow transplantation – bone marrow transplantation (also called hematopoietic cell transplantation) is being more seriously considered as a therapy for CLL, especially for patients under the age of 55. If it is performed, it is usually done after treatment with chemotherapy. Giving chemotherapy often induces a complete or partial remission.

Bone marrow transplantation is a treatment in which the patient is given high doses of chemotherapy or radiation. This kills cancer cells but also destroys all normal cells developing in the bone marrow. After the treatment, the patient needs to have a healthy

supply of very young blood cells, called stem cells, reintroduced or transplanted. The transplanted cells then re-establish the blood cell production process in the bone marrow.

There are two main types of stem cell transplant:

Allogeneic transplant – the patient is given stem cells from a donor, ideally a brother or sister with a similar genetic make-up. If the patient does not have a 'matched' sib ling, an unrelated person with a partially matched genetic make-up may be used.

Patients who are unable to tolerate high dose chemotherapy may be candidates for a reduced intensity transplant (called a mini-transplant or non-myeloablative transplant) from a relative or a matched unrelated donor, and may achieve long term control of the CLL.

Autologous transplant – the patient's own stem cells are removed before the high dose chemotherapy or radiation is given. Because the potential for cure with autologous transplantation is low for people with CLL, it is not usually recommended.

(Uptodate; National Cancer Institute; Cancer Research UK).

During 2017 the Food and Drug Administration (FDA) has approved Rituxan Hycela (rituximab and hyaluronidase human) for subcutaneous injection for the treatment of chronic lymphoblastic leukaemia. The product combines the CD20-directed cytolytic antibody rituximab with hyaluronidase human, an endoglycosidase that increases the permeability of the subcutaneous tissue allowing for increased absorption of rituximab.

Rituxan Hycela is also indicated for previously untreated and previously treated chronic lymphocytic leukaemia in combination with fludarabine and cyclophosphamide.
(MPR).

Prognosis (outlook) for Adult Chronic Lymphoblastic Leukaemia

The prognosis (chance of recovery) for patients with CLL depends on:

- Whether there is a change in the DNA and the type of change, if there is one
- Whether lymphocytes are spread throughout the bone marrow
- The stage of the disease
- Whether the CLL gets better with treatment or has recurred (come back)
- Whether the CLL progresses to lymphoma or prolymphoblastic leukaemia
- The patient's general health

(National Cancer Institute).

Supportive Care

Watch and Wait. People with CLL who have minimal changes in their blood counts and no symptoms are usually managed with observation alone. This approach includes medical examinations and periodic testing to determine whether the disease is stable or beginning to progress. People with CLL being treated with a watch and wait approach are counselled by their doctors to seek medical assistance if they develop fevers or other signs of infection or illness. When, or if, the disease begins to progress, active treatment is started.

People are often concerned when they receive a diagnosis of CLL and then learn that they will not begin treatment right away. It is important to know that the watch and wait approach is the current standard of care for people with CLL who have minimal changes in their blood counts and no symptoms. Many studies have compared the watch and wait approach to an early treatment approach for people with low-risk CLL. To date, no benefits of early treatment for people with low-risk CLL have been shown. Several studies have confirmed that the use of alkylating agents in patients with early-stage disease does not prolong survival. There are also risks of early treatment including potential side effects and treatment complications.

Patients may build up a resistance to the drugs used and would not be able to use them again when treatment for progressive disease is necessary. Deferred treatment versus early treatment for people with CLL who are symptom-free is an area of ongoing study in clinical trials.

Patients with CLL are often forced to live with the uncertainties associated with CLL. It can be puzzling and frightening to hear that one has CLL and that no treatment is recommended. Such individuals will benefit from psychological counselling to help them cope with the strong emotions that may accompany a diagnosis of CLL.

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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