Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet
on
Spinal Cord Cancer

Introduction

The human vertebral column (backbone or spine) consists of 24 articulating vertebrae and 9 fused vertebrae in the sacrum and the coccyx. The vertebrae are separated from each other by intervertebral discs. It houses and protects the spinal cord in its spinal canal.

The human vertebral column consists of 33 vertebrae in total. These are divided into different regions, which correspond to the curves of the spinal column. These regions are called the cervical spine (neck), thoracic spine (chest), lumbar spine (middle back), sacrum and coccyx (lower back). The articulating vertebrae are named according to the regions of the spine. There are seven cervical vertebrae, twelve thoracic vertebrae and five lumbar vertebrae. Vertebrae in these regions are essentially alike, with minor variation.

[Picture Credit: Picture of Spinal Cancer]

The number of vertebrae in a region can vary but overall the number remains the same. The number of those in the cervical region however is only rarely changed. Individual vertebrae are named according to their region and position. From top to bottom, the vertebrae are:

- Cervical spine: 7 vertebrae (C1–C7)
- Thoracic spine: 12 vertebrae (T1–T12)
- Lumbar spine: 5 vertebrae (L1–L5)
- Sacrum: 5 (fused) vertebrae (S1–S5)
- Coccyx: 4 (3–5) (fused) vertebrae (Tailbone)

(Wikipedia).

Spinal Cord Cancer

Spinal cord tumours are masses of abnormal cells that grow in the spinal cord, between its protective sheaths, or on the surface of the sheath that covers the spinal cord. Most non-

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic counselling; Diagnostic Radiographer; Dip Audiometry and Noise Measurement]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

cancerous tumours develop within the spinal cord rather than spreading from other parts of the body. These are called primary tumours, and they usually are non-cancerous (benign). Primary spinal cord cancers rarely spread to other parts of the body. This is unusual, which has made spinal cord cancers a focus of scientific investigation; their unique qualities may suggest new methods of cancer prevention or treatment.

Most cancerous spinal cord tumours are secondary, meaning they spread from a cancer at another site of the body. One in every four people whose cancer has spread throughout the body has had it spread to the brain or spinal cord. These secondary tumours most frequently result from lung, prostate or breast cancer.

Spinal cord tumours can affect people of all ages, but are seen most commonly in young and middle-aged adults.
(Drugs.com).

Incidence of Spinal Cord Cancer in South Africa
The National Cancer Registry (2013) does not provide any information regarding the incidence of Spinal Cord Cancer.

Symptoms of Spinal Cord Cancer
The most noticeable sign of spinal cancer is pain. Pain can come from the tumour's presence in the spinal column, pushing on sensitive nerve endings or causing spinal instability. When the spine is not lined up properly, other physically notable symptoms may result (e.g., changes in posture, Kyphosis or hunchback).

When the tumour presses on the spinal cord, symptoms may begin with numbness or tingling in the arms or legs. Next, there may be clumsiness, not knowing where the feet are, and difficulty with buttons or keys. As the disease progresses, spinal cancer symptoms may grow to include weakness, inability to move the legs and eventually paralysis.

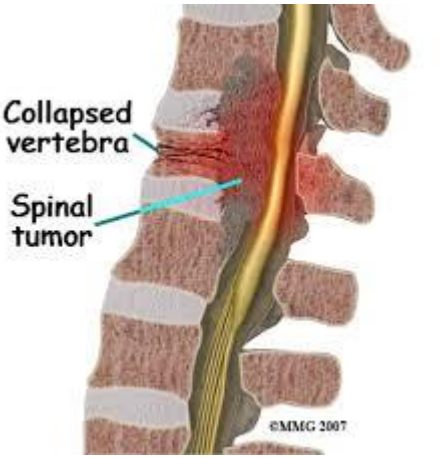
Some common signs of spinal tumours may include the following:

- Pain (back and/or neck pain, arm and/or leg pain)
- Muscle weakness or numbness in the arms or legs
- Difficulty walking
- General loss of sensation
- Difficulty with urination (incontinence)
- Change in bowel habits (retention)
- Paralysis to varying degrees
- Spinal deformities
- Pain or difficulty with standing
- Focal spine pain that is worse in the morning
- Pain that is severe when there is direct manipulation or compression of the affected area of the spine
- Back pain along with constitutional symptoms, such as loss of appetite, unplanned weight loss, nausea, vomiting, or fever, shills or shakes
- Decreased sensitivity to pain, heat and cold

(Cancer Treatment Centers of America; Spine-health; Mayo Clinic).

Types of Spinal Cord Tumours
Spinal cord tumours are classified according to their location in the spine.

The spinal cord is a long column of nerve fibres that carries messages to and from the brain. Wrapped around the entire spinal cord are three protective membranes knows as meninges. The outer layer is the dura mater, the middle layer is the arachnoid membrane and the innermost layer is the pia mater.



[Picture Credit: Spinal Cord Tumour]

Spinal cord tumours may be classified as intradural or extradural depending on where they occur relative to the protective membranes of the spinal cord. Intradermal tumours occur within the dura mater and are further divided into two sub-categories:

Extramedullary tumours – these tumours develop outside the spinal cord, such as in the surrounding dura mater (meningiomas) or in the nerve roots that extend out from the spinal cord (schwannomas and neurofibromas). These tumours are non-cancerous in most cases.

Intramedullary tumours – these tumours begin in the supporting cells within the spinal cord Most are either astrocytomas or ependymomas. In rare cases, intramedullary tumours from other parts of the body can spread through the bloodstream to the spinal cord itself.
(Mayo Clinic).

Primary Spinal Tumours
<u>Bone-producing tumours of the spine</u>
These include:

- Osteoid osteoma - benign and locally self-limiting:
  - Typically presenting in children aged 10-20 years - mostly males.
  - They involve the axial skeleton about 10% of the time.
  - Over half of osteoid osteomas are found in the lumbar region; the next most common site is the cervical region, then the thoracic region and then the least common site - the sacral region.
  - Osteoid osteomas are usually symptomatic.
  - They can result in painful scoliosis, muscular atrophy, radicular pain and gait disturbances secondary to pain and splinting.

- Osteoblastoma - benign but expand locally and are aggressive:
  - They occur in young patients in the second or third decade of life.
  - They are twice as common in males as they are in females.
  - Patients typically complain of dull localised pain and paraesthesiae.
  - There may be paraparesis and, if the tumour is large enough, paralysis.

- Giant cell tumours - most are benign:
  - Malignancy occurs in only a small minority of cases and is usually related to previous irradiation in the area of the tumour.
  - These are more common in women and occur in the third to fifth decades of life.
  - They can increase dramatically in size during pregnancy, secondary to hormonal influences.
  - The symptoms include pain with radicular pattern and neurological impingement with weakness and sensory deficits.

- Osteosarcoma - a malignant spindle cell lesion which produces osteoid, the organic portion of the bone matrix, secreted by osteoblasts:
  - Osteosarcomas of the spine are rare.
  - They typically present in patients in the fourth decade of life and have a male predominance.
  - Osteosarcomas are most common in the lumbosacral segments.
  - Patients often present with pain and a palpable mass.
  - Neurological symptoms are found in the majority of patients.
  - Serum alkaline phosphatase may be elevated.

<u>Cartilage-producing tumours of the spine</u>

- Osteochondroma - they also are commonly referred to as exostosis:
  - It is a benign lesion with cartilaginous cap.
  - Osteochondromas make up 4% of all solitary spine tumours.
  - They occur in patients aged 20-30 years.
  - They are more common in males.
  - Osteochondromas are more common in the cervical spine.

- Chondrosarcoma - malignant cartilage-producing tumours:
  - Chondrosarcoma is the second most common non-lymphoproliferative tumour of the spine.
  - Chondrosarcomas comprise about 10% of all spinal tumours.
  - Men are affected more often than women.
  - The mean age at presentation is about 45 years.
  - The thoracic spine is the most common site.
  - The most common symptoms are pain, a palpable mass and neurological complaints.

<u>Lymphoproliferative tumours</u>

- Multiple myeloma and plasmacytoma - multiple myeloma is the most common primary malignancy of bone and the spine:
  - Multiple myeloma is a systemic disease that affects middle-aged people and is characterised by areas of local bone destruction.
  - The underlying cell line is the malignant plasma cell, which produces abnormal quantities of immunoglobulins.
  - Patients complain of pain that may be worse at night.

- Lymphoma - this is associated with a large infiltrate of lymphoid cells.

Tumour of notochordal origin

- Chordoma - chordomas are uncommon tumours:
  - However, they are the most common primary malignant tumour of the spine in the adult, excluding lymphoproliferative tumours and metastases.
  - Presentation is often subtle with a gradual onset of pain, numbness, motor weakness and constipation or incontinence.
  - Constipation is a uniform finding in most patients with sacrococcygeal lesions.
  - Chordomas are slow-growing lesions and are often very large at the time of presentation.

Round cell tumour

- Ewing's sarcoma - Ewing's sarcoma is the most common non-lymphoproliferative primary malignant tumour of the spine in children:
  - Patients with Ewing's sarcoma usually present aged 10-20 years.
  - The most common site of occurrence in the spine is the sacrococcygeal region.

When classifying benign lesions they may be latent (stage 1), active (stage 2) or aggressive (stage 3).
(Patient.Info).

Spinal Cord Tumours in Children

In children, spinal cord tumours are often gliomas (including spinal ependymoma). It is also possible for children to get spinal cord neuroblastomas or Ewing's sarcomas. All of these are very rare.

As with adults, the main treatment is usually surgery. If the tumour is a slow growing type (low grade) this may be all the treatment a child needs.

If the surgeon cannot completely remove the tumour, or if it is a fast growing (high grade) type, then the child's doctor may suggest radiotherapy after surgery. If the child is very young, the doctor may suggest chemotherapy instead. Radiotherapy is then delayed until the child is over 3 years old. This is because radiotherapy can be particularly damaging to the nerves in very young children and may cause permanent side effects.

If the tumour comes back, the treatment will depend on the treatment the child had when their cancer was first diagnosed. It may be possible to operate again to remove more of the tumour. If the child did not have radiotherapy at first, the specialist may suggest it now. If the child did have radiotherapy first time round, it is usually not possible to have it again because it would cause too much damage to healthy tissue. The child's specialist may suggest chemotherapy instead.
(Cancer Research UK).

Risk Factors for Spinal Cord Cancer
Risk factors for spinal cord cancer include:

Prior history of cancer - cancers that may be more likely to spread to the spine include breast, lung, prostate and multiple myeloma.
Compromised immune system - some people whose immune systems are compromised develop spinal cord lymphomas.

Hereditary disorders - Von Hippel-Lindau disease and Neurofibromatosis (NF2) are inherited conditions that are sometimes associated with tumours in the spinal cord.

Exposures - exposure to radiation therapy or industrial chemicals may increase the likelihood of developing spinal cancer.
(Cancer Treatment Centers of America).

Diagnosis of Spinal Cord Cancer
Brain and spinal cord tumours are usually found because of signs and symptoms a person is having. If a tumour is suspected, tests will be needed to confirm the diagnosis.

Medical history - if signs or symptoms suggest one might have a brain or spinal cord tumour, the doctor will get a complete medical history, focusing on the symptoms and when they began. The doctor will also do a neurologic exam to check the brain and spinal cord function. It tests reflexes, muscle strength, vision, eye and mouth movement, coordination, balance, alertness, and other functions.

If the results of the examination are abnormal, the doctor may refer the patient to a neurologist (a doctor who specialises in medical treatment of nervous system diseases) or a neurosurgeon (a doctor who specialises in surgical treatment of nervous system diseases), who will do a more detailed neurologic examination or other tests.

Imaging Tests - the doctor may order one or more imaging tests. These tests use x-rays, strong magnets, or radioactive substances to create pictures of the brain and spinal cord. The pictures may be looked at by doctors specialising in this field (neurosurgeons, neurologists, and neuroradiologists) as well as by the primary doctor.

Magnetic resonance imaging (MRI) scan - MRI scans are very good for looking at the brain and spinal cord and are considered the best way to look for tumours in these areas. The images they provide are usually more detailed than those from CT scans (described below). But they do not image the bones of the skull as well as CT scans and, therefore, may not show the effects of tumours on the skull.

MRI scans use radio waves and strong magnets instead of X-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern into a very detailed image of parts of the body. A contrast material called *gadolinium* may be injected into a vein before the scan to help see details better.

MRI scans can take a long time - often up to an hour. The patient may have to lie on a table that slides inside a narrow tube, which can be confining and might upset people with a fear of enclosed spaces. The machine also makes buzzing and clicking noises that one may find disturbing. Some people might need medicine to help them relax for the test.

Magnetic resonance angiography (MRA) - this special form of MRI may be done to look at the blood vessels in the brain. This can be very useful before surgery to help the surgeon plan an operation.

Magnetic resonance spectroscopy (MRS) - this test is like an MRI, except that it measures radio wave interactions with different chemicals in the brain. MRS highlights some features of brain tumours that are not clearly seen by MRI. It creates graph-like results called *spectra* (although basic images can also be created). This might give clues as to the type of tumour, but in most cases a biopsy of the tumour is still needed to get an accurate diagnosis. MRS can also be used after treatment to help determine if an area that still looks abnormal on another test is remaining tumour or if it is more likely to be scar tissue.

Magnetic resonance perfusion - for this test, also known as *perfusion MRI*, a contrast dye is injected quickly into a vein. A special type of MR image is then obtained to look at the amount of blood going through different parts of the brain and tumour. Tumours often have a bigger blood supply than normal areas of the brain. A faster growing tumour may need more blood.

Perfusion MRI can give doctors an idea of the best place to take a biopsy. It can also be used after treatment to help determine if an area that still looks abnormal is remaining tumour or if it is more likely to be scar tissue.
Computed tomography (CT) scan - the CT scan is an X-ray test that produces detailed cross-sectional images of your brain and spinal cord (or other parts of the body). Instead of taking one picture, like a regular X-ray, a CT scanner takes many pictures as it rotates around the patient while he/she lies on a table. A computer then combines these pictures into images of slices of the body. Unlike a regular x-ray, a CT scan creates detailed images of the soft tissues in the body.

CT scans are not used as often as MRI scans when looking at brain or spinal cord tumours, but they can be useful in some cases. They may be used if MRI is not an option (such as in people who are very overweight or people who have a fear of enclosed spaces). CT scans also show greater detail of the bone structures near the tumour.

Before the scan, the patient may get an injection of a contrast dye through an IV (intravenous) line. This helps better outline any tumours that are present. The contrast may cause some flushing (a feeling of warmth, especially in the face). Some people are allergic and get hives. Rarely, people have more serious reactions like trouble breathing or low blood pressure.

A CT scanner has been described as a large donut, with a narrow table that slides in and out of the middle opening. One needs to lie still on the table while the scan is being done. Some people feel a bit confined by the ring while the pictures are being taken, although it is not as narrow as an MRI tube.

Positron emission tomography (PET) scan - for this test, a radioactive substance (usually a type of sugar known as *FDG*) is injected into the blood. The amount of radioactivity used is very low and passes out of the body within a day or so. Because tumour cells in the body

grow quickly, they absorb larger amounts of the sugar than most other cells. After about an hour, the patient is moved onto a table in the PET scanner. He/she lies on the table for about 30 minutes while a special camera creates a picture of areas of radioactivity in the body. The picture is not as detailed as a CT or MRI scan, but it can provide helpful information about whether abnormal areas seen on other tests (such as MRIs) are likely to be tumours or not.

This test is also useful after treatment to help determine if an area that still looks abnormal on an MRI scan is remaining tumour or if it is more likely to be scar tissue. Any remaining tumour will show up on the PET scan, while scar tissue will not.

Angiogram - for this test, a special dye is injected into blood vessels near the tumour, and the area is then viewed with x-rays. This helps doctors look at the blood supply of a tumour.

This test is not done much for brain or spinal cord tumours anymore, as it has largely been replaced by other tests that can look at blood vessels, such as computerised tomographic angiography (CTA) or magnetic resonance angiography (MRA).

Rarely, an angiogram may be used as part of the treatment for certain brain tumours. It is done as a first step of a procedure called *embolization*, in which the radiologist injects tiny particles into the blood vessels feeding the tumour to block them and make it easier to remove the tumour.
(American Cancer Society).

Grading of Spinal Cord Cancer
The grade describes the rate at which tumours grow and the likeliness or ability to spread into nearby tissue. Most central nervous system tumours do not spread in the body. However, the medical team may need to do other tests to check if the cancer has spread (e.g. CT or MRI scans, or checking the cerebrospinal fluid).

Brain and spinal cord tumours are usually given a grade on a scale of 1 to 4. The grade is worked out by looking at the tumour cells and comparing them to normal cells.

- Grades 1 and 2 – These are the slowest-growing tumours. They are called low-grade tumours.
- Grade 3 – Tumours grow at a moderate rate. They are called high-grade tumours.
- Grade 4 – These are the fastest-growing tumours. They are also called high-grade tumours.

(Cancer Council NSW).

Spinal Cord Tumour Treatment
Treatment of spinal cord tumours include:

Surgery - while surgery is increasingly recommended for benign and malignant primary spinal cord tumours, the role of surgery in spinal metastasis, or cancer that has spread to the spine, is controversial. Recent developments in imaging as well as new surgical tools and techniques, such as ultrasonic aspirators and lasers, have significantly expanded the role of surgery as an intervention.

For metastatic tumours with spinal cord compression, some neurosurgeons may perform surgery in selected patients to relieve pressure and pain, reconstruct or stabilise the spine, preserve mobility and bowel and bladder function, and to maximise quality of life. Some doctors may only recommend surgery for patients with a single metastatic tumour and no evidence of cancer growing at another site.

Radiation Therapy - most patients with primary spinal cord tumours will not require radiation therapy. Radiation, however, is used to treat spinal cord compression due to metastatic cancer or cancer that has spread from other locations. Other targets of radiation include some primary cancers of the spine and more rarely, benign or low-grade spinal cord tumours that cannot be completely removed surgically.

The spinal cord is even more sensitive to the effects of radiation than the brain. Radiation oncologists work carefully to minimise the risk of radiation-induced damage to normal spinal tissue since it can be progressive and irreversible. The thoracic spinal cord segments, or those located near the chest where half of all spinal tumours occur, are the most sensitive to the effects of radiation.

Radiosurgery with an advanced device called the CyberKnife may be an option for some patients. The CyberKnife is a painless, non-invasive treatment that delivers high doses of precisely targeted radiation to destroy tumours or lesions. Radiosurgery minimises radiation exposure to healthy tissue surrounding the tumour.

The CyberKnife uses a robotic arm to deliver highly focused beams of radiation. The flexibility of the robotic arm makes it possible to treat areas of the body, such as the spine and spinal cord, that cannot be treated by other radiosurgery techniques.

Chemotherapy - chemotherapy, similar to that used for brain tumours, may be recommended in adults for spinal gliomas that progress after surgery and radiation.

Chemotherapy is the use of drugs to kill cancer cells. The doctor may use just one drug or a combination, usually giving the drugs by mouth or by injection into a blood vessel or muscle. Intrathecal chemotherapy involves injecting the drugs into the cerebrospinal fluid.

Chemotherapy is usually given in cycles: a treatment period followed by a recovery period, then another treatment period, and so on. Patients often do not need to stay in the hospital for treatment. Most drugs can be given in the doctor's office or the outpatient clinic. However, depending on the drugs used, the way they are given and the patient's general health, a short hospital stay may be necessary.
(UCSF Medical Center).

Benign or Non-Cancerous Spinal Tumours
Spinal tumours that are usually benign - a benign tumour is not cancerous and will not spread to other parts of the body. Benign spinal tumours include:

- Neurofibromas
- Schwannomas
- Meningiomas

- Ependymomas
- Astrocytomas
- Hemangioblastomas
- Osteosarcomas
- Osteoid osteomas.

(The Spine Hospital).

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.

<u>Use of Placebos</u>

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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