Cancer Association of South Africa (CANSA)

Research • Educate • Support

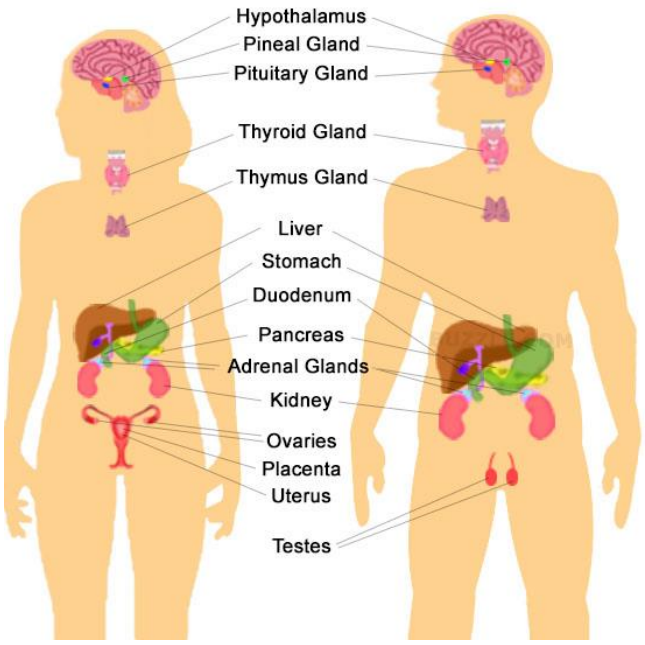
Fact Sheet on Pituitary Gland Cancer

Introduction

The endocrine system is a network of endocrine glands and nerves throughout the body. Endocrine glands produce and release hormones, which circulate around the body in the blood. Hormones keep an even balance of chemicals and fluid within the body and help the body respond to changes in the environment. Normally, the hormones released by endocrine glands are carefully balanced to meet the body's needs. There are many more organs in the body capable of secreting hormones than is popularly believed.

Endocrine organs (those capable of secreting hormones) include:

- Hypothalamus
- Pineal body
- Pituitary gland (anterior lobe)
- Pituitary gland (posterior lobe)
- Thyroid
- Alimentary system
  - Stomach
  - Duodenum
  - Liver
  - Pancreas
- Kidney
- Adrenal cortex
- Adrenal medulla
- Reproductive system
  - Testes
  - Ovaries
  - Placenta (during pregnancy)
  - Uterus (during pregnancy)
- Parathyroid
- Skin



[Picture Credit: Major Endocrine Organs]

(MacMillan Cancer Support; KidsHealth; MedLine Plus; Emedicinehealth; Wikipedia).

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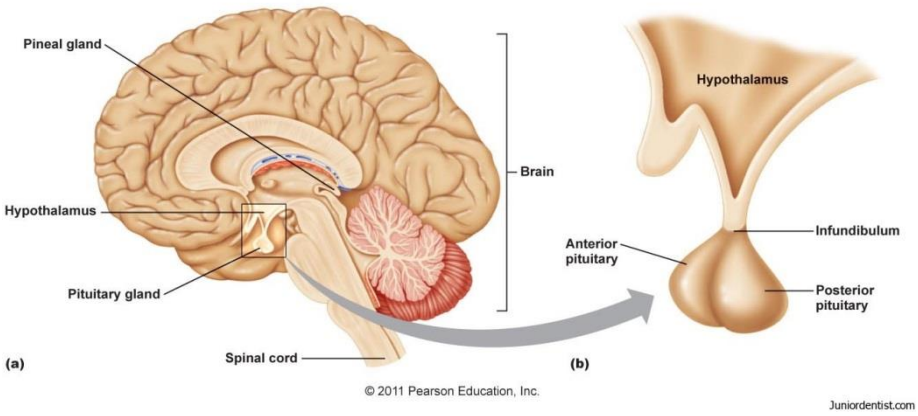
Pituitary Gland Cancer

When normal cells change and grow uncontrollably, they can form a mass called a tumour. A pituitary gland tumour can be benign (noncancerous and located only in the pituitary gland) or malignant (cancerous, meaning it can spread to other parts of the body). Most often, pituitary gland tumours are noncancerous growths and are called pituitary adenomas. However, a pituitary gland tumour can occasionally act like a cancerous tumour by growing into nearby tissue and structures, or rarely, spreading to other parts of the body.

[Picture Credit: Pituitary Gland]



Pituitary gland tumours are NOT brain tumours, as the pituitary gland is located under the brain and is separate from the brain. However, a tumour in this gland can be very serious because a pituitary gland that does not work can cause problems with other organs. The tumour can also press on nearby structures, such as the optic nerves, limiting a person's sight.

Incidence of Pituitary Gland Cancer in South Africa

The National Cancer Registry (2013) does not provide any information on the incidence of pituitary gland cancer. It combines all the endocrine cancers together.

According to the National Cancer Registry (2013) the following number of endocrine cancer 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	17	1:18 374	0,05%
Asian males	0	-	-
Black males	7	1:55 226	0,07%
Coloured males	2	1:8 700	0,05%
White males	7	1:3 759	0,04%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	25	1:15 192	0,07%
Asian females	0	-	-
Black females	11	1:31 642	0,07%
Coloured females	1	1:7 317	0,04%
White females	13	1:2 911	0,08%

The frequency of histologically diagnosed cases of endocrine cancer 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	12	0	1	1	1	2	0	0
Asian males	0	0	0	0	0	0	0	0
Black males	6	0	1	0	0	0	0	0
Coloured males	0	0	0	1	0	1	0	0
White males	5	0	0	0	1	1	0	0

Group - Females 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	11	4	1	2	4	0	1	2
Asian females	0	0	0	0	0	0	0	0
Black females	8	0	1	1	1	0	0	0
Coloured females	0	0	0	0	0	0	1	0
White females	3	2	1	1	3	0	0	2

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.

Signs and Symptoms of Pituitary Gland Cancer

A pituitary tumour can cause the pituitary gland to produce too much or too few hormones, which can cause problems in one's body. Large pituitary tumours - those measuring about 1cm - are known as macroadenomas. Smaller tumours are called microadenomas. Macroadenomas can put pressure on the rest of the pituitary gland and nearby structures.

Signs and symptoms of pressure from a pituitary tumour may include:

- Headache
- Vision loss, particularly loss of peripheral vision
- Nausea and vomiting
- Symptoms of pituitary hormone deficiency
- Weakness
- Less frequent or no menstrual periods
- Body hair loss
- Sexual dysfunction
- Increased frequency and amount of urination
- Unintended weight loss or gain

<u>Symptoms related to hormone level changes</u>

Some pituitary tumours, called functioning tumours, also produce hormones, generally causing an overproduction of hormones. Different types of functioning tumours can develop in the pituitary gland, each causing specific signs and symptoms and sometimes a combination of them.

<u>Adrenocorticotropic hormone-secreting (ACTH) tumours</u>

ACTH tumours produce the hormone adrenocorticotropin, which stimulates the adrenal glands to make the hormone cortisol. Cushing's syndrome results from the adrenal glands producing too much cortisol.

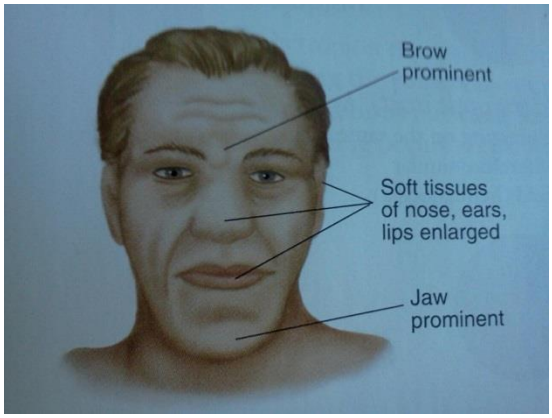
Signs and symptoms of Cushing's syndrome may include:

[Picture Credit: Cushing's]

- Fat accumulation around the midsection and upper back
- Exaggerated roundness of face
- A characteristic hump on the upper part of the back
- High blood pressure
- High blood sugar
- Muscle weakness
- Bruising
- Stretch marks
- Thinning of your skin
- Anxiety, irritability or depression

Growth hormone-secreting tumours

These tumours produce excess growth hormone. The effects from excess growth hormone (acromegaly) may include:



- Coarsened facial features
- Enlarged hands and feet
- Excess sweating
- High blood sugar
- Heart problems
- Joint pain
- Misaligned teeth
- Increased growth of body hair

[Picture Credit: Acromegaly]

Accelerated and excessive linear growth may occur in children and adolescents.

Prolactin-secreting tumours

Overproduction of prolactin from a pituitary tumour (prolactinoma) can cause a decrease in normal levels of sex hormones — oestrogen in women and testosterone in men. Excessive prolactin in the blood can affect men and women differently.

In women, prolactinoma may cause:

- Irregular menstrual periods
- Lack of menstrual periods
- Milky discharge from the breasts

In men, a prolactin-producing tumour may cause male hypogonadism. Signs and symptoms may include:

- Erectile dysfunction (ED)
- Infertility
- Loss of sex drive

Thyroid-stimulating hormone-secreting tumours

When a pituitary tumour overproduces thyroid-stimulating hormone, your thyroid gland makes too much of the hormone thyroxine. This is a rare cause of hyperthyroidism or overactive thyroid disease. Hyperthyroidism can accelerate your body's metabolism, causing:

- Sudden weight loss
- Rapid or irregular heartbeat
- Nervousness or irritability
- Frequent bowel movements
- Feeling warm or hot

(Mayo Clinic).

Staging of Pituitary Gland Cancer

Staging is a way of describing where a tumour is located, if or where it has spread, as well as whether it is affecting the functions of other organs in the body. Doctors use diagnostic tests to determine the tumour's stage, so staging may not be complete until all of the tests are finished. Knowing the stage helps the doctor to decide what kind of treatment is best and can help predict a patient's prognosis (chance of recovery). There are different stage descriptions for different types of tumours.

Because a pituitary gland tumour is most commonly noncancerous and called a pituitary adenoma, it is usually classified according to its size on an MRI (see Diagnosis).

- A microadenoma is small (10 millimeters [mm] or less)
- A macroadenoma is larger and can extend outside the *sella turcica* (the bony structure around the pituitary gland). A macroadenoma is larger than 10 mm at its widest point

Other factors considered when classifying a pituitary gland tumour include whether the tumour is functional (meaning, what, if any, hormone(s) it makes) and whether it has grown into nearby structures (most commonly, the cavernous sinus, an area near the pituitary gland that contains the carotid artery and several important nerves that control eye movement).
(Cancer.Net; American Cancer Society).

Diagnosis of Pituitary Gland Cancer

Pituitary tumours are usually found when a person goes to the doctor because of symptoms they are having. If there is a reason to suspect that a person might have a pituitary tumour, the doctor will use one or more tests to find out. Signs and symptoms might suggest that the person could have a pituitary tumour, but tests are needed to confirm the diagnosis.

If the symptoms lead a doctor to believe that a person might have a pituitary tumour, the first step is to take a complete medical history to check for risk factors and to learn more about the symptoms. The doctor may ask about the patient's family history of tumours or other problems to see if the patient might have an inherited genetic syndrome, such as multiple endocrine neoplasia, type I (MEN1).

The doctor will also do a physical examination to look for possible signs of a pituitary tumour or other health problems. This may include an examination to look for nervous system problems that could be caused by a tumour.

If a pituitary tumour is strongly suspected, the doctor may refer the patient to an ophthalmologist to check the patient's vision, as pituitary tumours can damage nerves leading to the eyes. The most common test is to measure how well the person can see. The doctor may also test the field of vision (or visual fields). At first, pituitary tumours only press on part of the optic nerves. This leads to parts of a person's vision being lost. This is usually the peripheral vision, meaning things that one can see off to the side without actually looking directly at them. Ophthalmologists have special instruments that can test for this.

The symptoms and physical examination results may lead the doctor to believe that a patient might have a pituitary tumour. If the doctor suspects a hormone-producing tumour, hormone levels in the blood and/or urine will be measured.

Growth hormone-secreting adenoma - the next step is to check for excess growth hormone production. Levels of growth hormone and insulin-like growth factor-1 (IGF-1) will be measured in blood samples, which are taken the morning after an overnight fast. When growth hormone levels are high, it cause the liver to make more IGF-1. Testing the IGF-1 level can be more helpful than checking the level of growth hormone, as the IGF-1 level doesn't change much during the day, while the level of growth hormone can go up and down.

If both levels are very high, the diagnosis is clearly a pituitary tumour. If the levels are slightly increased, another test called a *glucose suppression test* is often done to be sure. A patient will be asked to drink a sugary liquid and the levels of growth hormone and blood sugar will be measured at intervals afterward. The normal response to suddenly taking in so much sugar is a drop in growth hormone levels. If the growth hormone levels remain high, a pituitary adenoma is probably the cause.

Corticotropin (ACTH)-secreting adenoma - most of the signs and symptoms of ACTH-secreting tumours come from having too much cortisol (an adrenal steroid hormone). Quite a few diseases can cause the body to make too much cortisol. Patients with symptoms suggesting this condition need tests to determine if a pituitary tumour is the cause.

These tests may include measuring levels of cortisol and ACTH in blood samples taken at different times of the day. The patient may be asked to collect all the urine that they produce over a 24-hour period, which is then tested to measure daily production of cortisol and other steroid hormones. Blood or urine cortisol levels may be checked again after taking a dose of a powerful, cortisone-like drug called dexamethasone. Levels of cortisol in the saliva late at night can also be checked. These tests help to distinguish patients with ACTH-secreting pituitary tumours from patients with other diseases, such as adrenal gland tumours, that may cause similar symptoms.

Prolactin-secreting adenoma (prolactinoma) - blood prolactin levels can be measured to check for a prolactinoma.

Gonadotropin-secreting adenoma - luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels can be checked to see if a patient has a gonadotropin-secreting tumour. Levels of related hormones, such as estrogen, progesterone and testosterone, are often checked as well.

Thyrotropin-secreting adenoma - tests to measure blood levels of thyrotropin (TSH) and thyroid hormones can usually identify people with a thyrotropin-secreting adenoma.

Non-functional (null cell) adenoma - a pituitary adenoma is considered non-functional if it does not make too much of a pituitary hormone. Pituitary hormone levels are not high in people with non-functional tumours.

Sometimes, though, blood levels of some pituitary hormones may actually be low because the adenoma crowds out the cells that normally make these hormones.

Testing for diabetes insipidus - diabetes insipidus is caused by damage to the part of the pituitary that stores the hormone vasopressin (ADH). This condition can be caused by pituitary macroadenomas and carcinomas in rare cases, or by tumours starting in parts of the brain or nerves next to the pituitary gland. It can also be a side effect of surgery to treat pituitary tumours or tumours next to the pituitary gland.

In many cases, this diagnosis is made with tests that measure sodium levels in the blood and *osmolality* (total salt concentration) of the blood and urine. If these tests are inconclusive, then a water deprivation study may be done. In this test, you are not allowed to drink fluids for several hours.

The test is often done overnight. If your body is not making enough vasopressin, you will continue to make urine even though you are not taking in any fluid. You may also be given an injection of vasopressin to see if this corrects the problem.

Imaging tests

Imaging tests use x-rays, magnetic fields, or other means to create pictures of the inside of your body. They may be done to look for pituitary tumours or to see if they have grown into nearby structures. In some cases, an imaging test of the head done for another reason may detect a pituitary tumour.

Magnetic resonance imaging (MRI) scan - MRI scans use radio waves and strong magnets to create detailed pictures of the inside of the body. The energy from the radio waves is absorbed and then released in a pattern formed by the type of 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* is sometimes injected into a vein to improve the quality of the image.

MRI scans are very helpful in looking at the brain and spinal cord and are considered to be the best way to identify pituitary tumours of all types. The images they provide are usually more detailed than those from CT scans (see below). MRI can show macroadenomas of the

pituitary gland, as well as most microadenomas. But MRI may not be able to detect microadenomas that are smaller than 3 mm (about 1/8 inch) across. Sometimes the MRI scan will show a small abnormality in the pituitary that has nothing to do with the patient's symptoms. Between 5% and 25% of healthy people have some minor abnormality of the pituitary gland that shows up on an MRI scan.

MRI scans can take a long time – often up to an hour. The patient has to lie inside a narrow tube, sometimes with a small frame around the head, which can be confining and may upset people with a fear of enclosed spaces. Newer, open MRI machines may help with this, but they may provide less detailed images and can't be used in all cases. The machine also makes buzzing and clicking noises that may be disturbing. Some people may need medicine to help them relax for the test.

Computed tomography (CT) scan - the CT scan is an x-ray test that creates detailed cross-sectional images of part of the body. Instead of taking one picture, like a standard x-ray, a CT scanner takes many pictures as the camera rotates around the patient while he/she lies on a table. A computer then combines these pictures into an image of a slice of the body. Unlike a regular x-ray, a CT scan creates detailed images of the soft tissues in the body.

A CT scanner has been described as a large donut, with a narrow table in the middle opening. The patient will need to lie still on the table while the scan is being done. CT scans take longer than regular x-rays, and the patient might feel a bit confined by the ring while the pictures are being taken.

Before the test, one may get an injection of a contrast dye through an IV (intravenous) line. This helps better outline any tumours that are present. The injection can cause some flushing (redness and warm feeling). A few people are allergic to the dye and get hives or, rarely, have more serious reactions like trouble breathing and low blood pressure. Be sure to tell the doctor of any allergies or the occurrence of a reaction to any contrast material used for x-rays.

CT scans can find a pituitary adenoma if it is large enough, but MRI scans are used much more often to look at the brain and pituitary gland.

Tests of pituitary tissue samples - in diagnosing tumours of most parts of the body, imaging tests and blood tests may strongly suggest a particular type of tumour, but a *biopsy* (taking a sample of the tumour to examine under the microscope) is usually the only way to be certain of that diagnosis. In many situations, doctors will not treat the tumour until a biopsy has been done.

A pituitary tumour is an exception to this general rule in that a biopsy is not usually needed before treatment. One reason is that the hormone tests for some types of adenomas are very accurate, so a biopsy is not likely to provide much more information. Biopsies in this part of the body can also pose a very small risk of serious side effects. On top of this, some types of adenomas can be treated without surgery, using medicines or radiation therapy.

When pituitary tumours are removed by surgery, they are examined under a microscope to determine their exact type. Special stains may be used to color the areas making hormones, which helps classify the tumour.
(American Cancer Society).

Treatment of Pituitary Gland Cancer
The prognosis (chance of recovery) depends on the type of tumour and whether the tumour has spread into other areas of the central nervous system (brain and spinal cord) or outside of the central nervous system to other parts of the body.

Treatment options depend on the following:

- The type and size of the tumour
- Whether the tumour is making hormones
- Whether the tumour is causing problems with vision or other symptoms
- Whether the tumour has spread into the brain around the pituitary gland or to other parts of the body
- Whether the tumour has just been diagnosed or has recurred (come back)

(National Cancer Institute).

Treatment options and recommendations depend on several factors, including the type and stage of the tumour, possible side effects, and the patient's preferences and overall health. Learn more about making treatment decisions.

Active surveillance - active surveillance is an option for some people with a pituitary gland tumour who have no symptoms from the tumour and have hormones that work normally. During active surveillance, the tumour is monitored closely with periodic examinations and tests. Treatment would begin only if the tumour started causing symptoms.

Surgery - surgery is the removal of the tumour and surrounding tissue during an operation. It is the most common treatment for a pituitary gland tumour. Surgery for a pituitary gland tumour is often successful in removing the entire tumour. About 95% of surgeries to remove pituitary gland tumours are done by the transsphenoidal route (through the nasal passage, going along the septum that separates the two nostrils, then through the sphenoid sinus cavity located deep above the back of the throat to the pituitary gland immediately behind it). The rest are done through a craniotomy (an opening in the skull). This can be done using a microscope or an endoscope (a long flexible tube), or both, so the surgeon can see the tumour. Both of these methods are equally safe and effective when done by a skilled surgeon. Talk with your surgeon beforehand to learn about possible side effects based on the type of surgery you will have. Learn more about surgery for a tumour.

Because of the complex structure of the cranial base and its close proximity to cranial nerves and vessels, surgery in this area is associated with considerable risk of morbidity and mortality. The greatest disadvantages of the transethmoidal/transsphenoidal route are the approach and the external scar. The greatest advantages are the shorter route than in the transseptal approach (operating through the nose), the absence of endonasal complications and the minimal postoperative discomfort.

Complications include postoperative cerebrospinal fluid leakage and amaurosis (vision loss or weakness) and ophthalmoplegia of the heterolateral eye where the affected eye shows impairment of adduction (drawing inward toward the median axis of the body).

Radiation therapy - radiation therapy is the use of high-energy x-rays or other particles to kill tumour cells. A doctor who specializes in giving radiation therapy to treat a tumour is called a radiation oncologist. The most common type of radiation treatment is called external-beam radiation therapy, which is radiation given from a machine outside the body. A radiation therapy regimen (schedule) usually consists of a specific number of treatments given over a set period of time.

For some patients, stereotactic radiation therapy (delivering a high dose of radiation directly to the tumour) is used when any part of the tumour is left after surgery. Not all patients with part of a tumour remaining after surgery need radiation therapy because some noncancerous pituitary gland tumours do not grow back even when some tumour is left behind after surgery. If the entire tumour is removed, then radiation therapy is not needed.

Side effects from radiation therapy include fatigue, mild skin reactions, and upset stomach. Most side effects go away soon after treatment is finished. Depending on where the radiation therapy is directed, it may also cause vision problems and short-term memory or cognitive (thought-process) changes. However, the risk of developing vision problems or short-term memory or cognitive changes from radiation treatment is small because advances in external-beam radiation therapy allow doctors to aim the radiation more directly at the pituitary gland, sparing more of the surrounding normal tissue from the effects of radiation. Radiation therapy can cause the pituitary gland to gradually lose the ability to make hormones after treatment ends. If this occurs, hormone replacement therapy (see below) may be needed.

Hormone replacement therapy (HRT) - HRT is often necessary for patients with a pituitary tumour, and this may include replacement of thyroid and adrenal hormones, growth hormone, and/or testosterone in men or estrogen in women.

Drug therapy - the drugs bromocriptine (Parlodel) and cabergoline (Dostinex) are used to treat tumours that secrete prolactin, and octreotide (Sandostatin, OncoLAR) or pegvisomant (Somavert) can be used to treat tumours that make growth hormone. Octreotide can also be used to treat patients with pituitary tumours that secrete thyroid-stimulating hormone.
The medications used to treat pituitary tumours are continually being evaluated. Talking with your doctor is often the best way to learn about the medications you've been prescribed, their purpose, and their potential side effects or interactions with other medications. Learn more about your prescriptions by using searchable drug databases.

Supportive care - a tumour and its treatment often cause side effects. In addition to treatment to slow, stop, or eliminate the tumour, an important part of care is relieving a person’s symptoms and side effects. This approach is called palliative or supportive care, and it includes supporting the patient with his or her physical, emotional, and social needs.

Palliative care can help a person at any stage of illness. People often receive treatment for the tumour and treatment to ease side effects at the same time. In fact, patients who receive

both often have less severe symptoms, better quality of life, and report they are more satisfied with treatment.
(Cancer.Net).

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.

<u>Possible benefits of taking part in a clinical trial</u>

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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