

# Cancer Association of South Africa (CANSA)



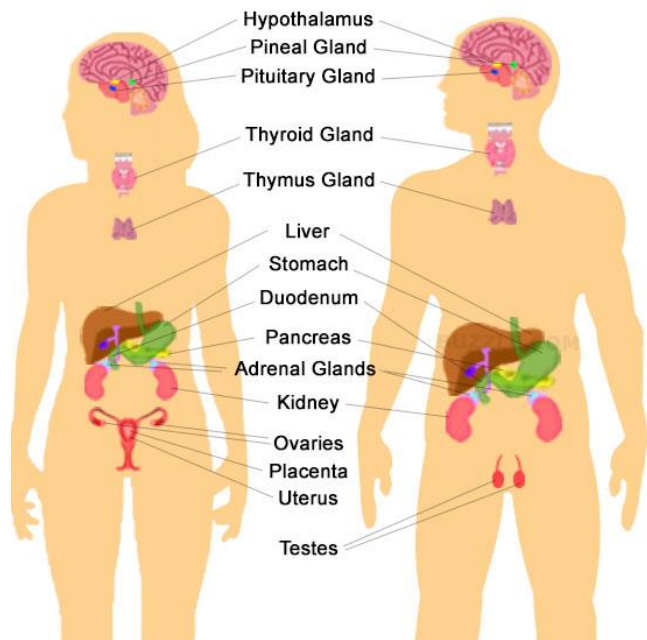
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## Fact Sheet on Adrenal Gland Cancer

### 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.

[Picture Credit: Major Endocrine Organs]



Endocrine organs (those organs that secrete 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

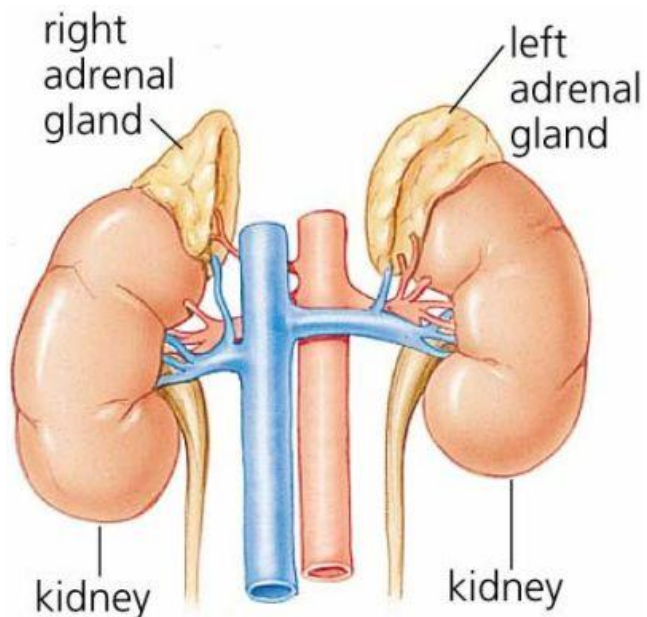
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(MacMillan Cancer Support; KidsHealth; MedLine Plus; Emedicinehealth; Wikipedia).

### Adrenal Gland Cancer

A tumour begins when normal cells change and grow uncontrollably, forming a mass. A tumour can be benign (noncancerous) or malignant (cancerous, meaning it can spread to other parts of the body).

Each person has two adrenal glands - one located on top of each of the body's two kidneys. These glands are important to the body's endocrine (hormonal) system. Each adrenal gland has two main parts that function separately:

[Picture Credit: Adrenal Gland]



Adrenal cortex - the outer part of the adrenal gland is called the cortex. The adrenal cortex makes three main hormones: cortisol, aldosterone, and dehydroepiandrosterone (also known as androstenolone or prasterone, as well as 3β-hydroxyandrost-5-en-17-one or 5-androsten-3β-ol-17-one or DHEA) is an important endogenous steroid hormone. These hormones carefully control metabolism and body characteristics, such as hair growth and body shape.

Adrenal medulla - the inner part of the gland is called the medulla. The adrenal medulla produces other hormones: epinephrine, norepinephrine and dopamine. These hormones control the body's responses to stress, including the 'fight or flight' adrenaline surge.

### Incidence of Adrenal Gland Cancer in South Africa

The National Cancer Register of 2012 does not provide any statistics regarding the incidence of adrenal gland cancer in South Africa.

According to the National Cancer Registry (2012) the following number of endocrine cancer cases was histologically diagnosed in South Africa during 2012:

Group - Males 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	37	1:6 570	0,10%
Asian males	1	1:4 447	0,17%
Black males	21	1:10 550	0,18%
Coloured males	4	1:6 286	0,10%
White males	11	1:2 694	0,05%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	26	1:14 357	0,07%
Asian females	0	-	-
Black females	17	1:18 807	0,10%
Coloured females	2	1:20 861	0,05%
White females	7	1:5 113	0,04%

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

Group - Males 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	8	8	3	6	6	4	2	0
Asian males	0	0	0	0	0	1	0	0
Black males	7	6	0	2	4	0	0	0
Coloured males	0	2	0	2	0	0	0	0
White males	1	0	3	2	1	1	2	0

Group - Females 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	15	1	2	3	2	2	1	0
Asian females	0	0	0	0	0	0	0	0
Black females	12	1	0	2	0	1	0	0
Coloured females	2	0	0	0	0	0	0	0
White females	1	0	1	1	2	1	0	0

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

## Types of Adrenal Gland Tumours

An adrenal gland tumour can sometimes overproduce hormones. When it does, the tumour is called a functioning tumour. An adrenal gland tumour that does not produce hormones is called a nonfunctioning tumour. A tumour can start in an adrenal gland (called a primary adrenal tumour), or it can begin in another organ, such as the lungs, and then metastasise (spread) to the adrenal glands. The symptoms and treatment of an adrenal gland tumour depend on whether the tumour is functioning or nonfunctioning, what hormone(s) is overproduced, as well as whether the tumour is a primary adrenal gland tumour or a metastases from cancer of another organ.

Primary adrenal gland tumours include the following:

- Adenoma - the most common type of adrenal gland tumour, making up the majority of all adrenal gland tumours. It is a noncancerous, nonfunctioning tumour of the adrenal cortex. Also called an adrenocortical adenoma, this tumour usually does not cause symptoms and, if it is small, often does not need treatment.
- Adrenocortical carcinoma - although rare, the most common type of cancerous adrenal gland tumours begins in the cortex and is called adrenocortical carcinoma, or adrenal cortical carcinoma. Approximately 4 to 12 out of one million people develop this type of tumour. Adrenocortical carcinoma can be a functioning or nonfunctioning tumour. If the tumour is functioning, it may produce more than one hormone.
- Neuroblastoma - this is a type of childhood cancer that can begin in the adrenal medulla.

- Pheochromocytoma - this type of neuroendocrine tumour most often begins in the adrenal medulla.

### Signs and Symptoms

Many patients will seek medical attention with some sort of bodily change which typically comes on quite slowly (usually over 1 to 3 years). When excess female hormones are produced in a female it can be hard to detect, except at extremes of age such as early puberty in a child, or the return of vaginal bleeding in a post-menopausal woman.

The same is true for excess testosterone in a male.

The opposite, however, will often make the presentation easier such as when a woman begins to develop male characteristics (deeper voice, excess body hair) or when a man begins to develop enlarged breasts.

Some of these hormone overproduction problems have specific names and are listed below:

- hypercortisolism (Cushing's syndrome) (excess cortisol produced)
- adrenogenital syndrome (excess sex steroids produced)
- virilisation (acquisition of male traits in a female because of excess testosterone production)
- feminisation (acquisition of female traits in a male because of excess oestrogen production)
- precocious puberty (puberty occurring too early because of excess sex steroids produced)
- hyperaldosteronism (Conn's syndrome) (excess aldosterone leading to hypertension and low potassium)

(EndocrineWeb).

### Diagnosis of Adrenal Gland Cancer

The following are employed in the diagnosis of adrenal gland cancer:

Laparoscopy - this procedure uses a laparoscope, a thin, flexible tube with a tiny video camera on the end. It is inserted through a small surgical opening in the patient's side to allow the surgeon to see where the cancer is growing. It can spot distant spread as well as enlarged lymph nodes. Sometimes it is combined with ultrasound to give a better picture of the cancer.

[Picture Credit: Laparoscope]



Laparoscopy may be done to help predict whether it will be possible to completely remove the cancer by surgery. In addition to viewing adrenal tumours through the

laparoscope, surgeons may sometimes remove small benign adrenal tumours through this instrument.

Biopsy - imaging tests may find tumours, but often the only way to know for sure that a tumour is cancerous is to remove a sample of tumour tissue to look at under the microscope. This is called a *biopsy*. If a thin needle that only removes tiny bits of tissue is used, it is called a *fine needle aspiration*, or FNA for short. When a larger needle that removes a thin cylindrical core of tissue is used, it is called a *core needle biopsy*. In either case, the biopsy is often done using a CT scan or ultrasound to guide the tip of the needle into the tumour.

Since adrenal adenomas and cancers can look alike under the microscope, a biopsy may not be able to tell whether or not an adrenal tumour is cancerous. Also, a needle biopsy of an adrenal cancer can actually spread tumour cells. For these reasons, a biopsy is generally not done before surgery if an adrenal tumour's size and certain features seen on imaging tests suggest it is cancer. Work-up with blood tests for hormone production and imaging studies are more useful than biopsies in the diagnosis of adrenal cancerous.

If the cancer appears to have metastasised (spread) to another part of the body such as the liver, then a needle biopsy of the metastasis may be done. If a patient is known to have an adrenal tumour and a liver biopsy shows adrenal cells are present in the liver, then the tumour is cancer.

In general, a biopsy is only obtained in a patient with adrenal cancer when there are tumours outside the adrenals and the doctor needs to know if these are spread (metastases) from an adrenal cancer or are caused by some other cancer or disease. Adrenal tumours are sometimes biopsied when the patient is known to have a different type of cancer (like lung cancer) and knowing that there is spread to the adrenal glands would alter treatment.

Tests for adrenal hormones - blood and urine tests to measure levels of adrenal hormones are important in deciding whether a patient with signs and symptoms of adrenal cancer has the disease. For urine tests, a person may be asked to collect all urine for 24 hours. Blood and urine tests are as important as imaging studies in the diagnostic work-up of adrenal cancer. Doctors choose which tests to do based on the patient's symptoms. Doctors know which symptoms are associated with high levels of certain hormones, so they can focus on ways to look for the hormones most likely to be affected. Often doctors will check hormone levels even when symptoms of high hormone levels are not present. This is because symptoms of abnormal hormone levels can be very subtle and blood tests may even be able to detect changes in hormone levels before symptoms occur.

Tests for high cortisol levels - the tests used in this case include measuring levels of cortisol in the blood and in the urine. If an adrenal tumour is producing cortisol, these levels will be abnormally high. These tests may be done after giving the patient a dose of dexamethasone. Dexamethasone is a drug that acts like cortisol. If given to someone who does not have an adrenal tumour, it will decrease production of cortisol and similar hormones. In someone with an adrenal cortex tumour, these hormone levels will remain high after they receive dexamethasone. Blood levels of ACTH will also be measured to help distinguish adrenal tumours from other diseases that can cause high cortisol levels.



Tests for high aldosterone levels - the level of aldosterone will be measured and will be high if the tumour is making aldosterone. Also, high aldosterone leads to low levels of potassium and renin (a hormone produced by the kidneys) in their blood.

Tests for high androgen or estrogen levels - patients with androgen-producing tumours will have high levels of dehydroepiandrosterone sulfate (DHEAS) or testosterone and patients with estrogen-producing tumours will have high levels of estrogen in their blood.

The following imaging tests are also done:

Chest X-ray - this can show if the cancer has spread to the lungs. It may also be useful to determine if there are any serious lung or heart diseases.

Ultrasound - ultrasound tests use sound waves to take pictures of parts of the body. A device called a transducer produces the sound waves, which are reflected by tissues of nearby organs. The pattern of sound wave echoes is detected by the transducer and analysed by a computer to create an image of these tissues and organs. This test can show if there is a tumour mass in the adrenal gland. It can also diagnose tumour masses in the liver if the cancer has spread there. In general, it is not used to look for adrenal tumours unless a CT scan isn't able to be done.

Molecular markers - studies analysing the role of genes and proteins in a person's tumour are underway. The focus of these studies is to help fine-tune the diagnosis of adrenal gland tumours and predict treatment results (Cancer.Net).

Computed tomography (CT) - the CT scan is an x-ray procedure that produces detailed cross-sectional images of your body. Instead of taking one picture, like a conventional x-ray, a CT scanner takes many pictures as the camera rotates around you. A computer then combines these pictures into an image of a slice of your body. The machine will take pictures of many slices of the part of your body that is being studied.

CT scans show the adrenal glands fairly clearly and often can confirm the location of the cancer. It can also help show whether the cancer has spread into the liver or other organs nearby. CT scans can also show lymph nodes and distant organs where metastatic cancer might be present. The CT scan can help determine if surgery is a good treatment option.

Before any pictures are taken, a person may be asked to drink 1 to 2 pints of a liquid called *oral contrast*. This helps outline the intestine so that certain areas are not mistaken for tumours. You may also receive an IV (intravenous) line through which a different kind of contrast dye (IV contrast) is injected. This helps better outline structures in the body.

The injection can cause some flushing (redness and warm feeling that may last hours to days). A few people are allergic to the dye and get hives. Rarely, more serious reactions like trouble breathing and low blood pressure can occur. Medicine can be given to prevent and treat allergic reactions. Patients must inform the treating doctor if they have ever had a reaction to any contrast material used for x-rays.

CT scans can also be used to precisely guide a biopsy needle into a suspected metastasis. For this procedure, called a *CT-guided needle biopsy*, the patient remains on the CT

scanning table, while a radiologist moves a biopsy needle toward the location of the mass. CT scans are repeated until the doctors are sure that the needle is within the mass. A fine needle biopsy sample (tiny fragment of tissue) or a core needle biopsy sample (a thin cylinder of tissue about 12mm long and less than 3mm in diameter) is removed and examined under a microscope.

CT scans take longer than regular x-rays. One needs to lie still on a table while this is being done. During the test, the table slides in and out of the scanner, a ring-shaped machine that completely surrounds the table. One might feel a bit confined by the ring one has to lie in while the pictures are being taken.

Positron emission tomography (PET) - in this test, radioactive glucose (sugar) is injected into the patient's vein. Because cancer cells use sugar much faster than normal tissues, radioactivity will tend to concentrate in the cancer. A scanner can spot the radioactive deposits. This test can be helpful for spotting small collections of cancer cells and may be used to find cancer that has spread. It also may help in deciding if an adrenal tumour is likely to be benign or malignant (cancer).

A special type of PET scan is currently used in research settings. It uses a radioactive form of a substance called *metomidate*. This substance seems to concentrate in adrenal cortical tissue, particularly adenomas and carcinomas. PET scanning with metomidate may, in the future, be helpful in distinguishing tumours that start in the adrenal cortex from cancers that started in other organs and then spread to the adrenals. It may also be helpful in finding adrenal cancer that has spread outside the adrenals.

Magnetic resonance imaging (MRI) - 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 tissue and by certain diseases. A computer translates the pattern of radio waves given off by the tissues into a very detailed image of parts of the body. Not only does this produce cross sectional slices of the body like a CT scanner, it can also produce slices that are parallel with the length of the body. For some MRI scans, a contrast material called *gadolinium* is injected into a vein (IV). MRI may sometimes provide more information than CT scans because it can better distinguish adrenal cancers from benign tumours.

A MRI scan is particularly helpful in examining the brain and spinal cord. In people with suspected adrenal tumours, an MRI of the brain may be done to examine the pituitary gland. Tumours of the pituitary gland, which lies underneath the front of the brain, can cause symptoms and signs similar to adrenal tumours.

A MRI scan is a little more uncomfortable than a CT scan. It often takes up to an hour. One has to be placed inside a tube, which is confining and can upset people who become anxious in tight spaces (claustrophobia). If you have problems with tight spaces, tell your doctor before your MRI. Medicine may be given before the scan to help with anxiety. If that doesn't work, the exam may be scheduled at an open MRI scanner. These machines are not so enclosing and so are easier for some patients, although the drawback is that the pictures may not be as good. The machine also makes a thumping noise that may be disturbing to the patient. Some places will provide headphones with music to block this sound out. (American Cancer Society).

## Staging of Adrenal Gland Cancer

Staging is a way of describing where the tumour is located, if or where it has spread and 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 before all test and even the surgical removal of the tumour or adrenal gland, are done. 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 cancer.

One tool that doctors use to describe the stage is the TNM system. This system judges three factors: the tumour itself, the lymph nodes around the tumour, as well as whether the tumour has spread to other parts of the body. The results are combined to determine the stage of cancer for each person. There are four stages for adrenocortical carcinoma: stages I through IV. The stage provides a common way of describing the cancer, so doctors can work together to plan the best treatments.

TNM is an abbreviation for tumour (**T**), node (**N**), and metastasis (**M**). Doctors look at these three factors to determine the stage of cancer:

- How large is the primary tumour and where is it located? (**Tumour, T**)
- Has the tumour spread to the lymph nodes? (**Node, N**)
- Has the cancer metastasized to other parts of the body? (**Metastasis, M**)

**Tumour.** Using the TNM system, the 'T' plus a letter or number (0 to 4) is used to describe the size and location of the tumour. Some stages are also divided into smaller groups that help describe the tumour in even more detail. Specific tumour stage information is listed below.

**TX:** The primary tumour cannot be evaluated

**T0:** There is no primary tumour

**T1:** The tumour is 5 centimeters (cm) or less and has not grown outside of the adrenal gland

**T2:** The tumour is larger than 5 cm and has not grown outside of the adrenal gland

**T3:** The tumour is any size, and it has grown into the area around the adrenal gland but not to nearby organs

**T4:** The tumour is any size and has grown into nearby organs, such as the kidney; diaphragm (the thin muscle under the lungs and heart that separates the chest from the abdomen); larger blood vessels, called the aorta and the vena cava; pancreas; spleen; and liver.

**Node.** The 'N' in the TNM staging system stands for lymph nodes, the tiny, bean-shaped organs that help fight infection. Lymph nodes near where the tumour started are called regional lymph nodes. Lymph nodes in other parts of the body are called distant lymph nodes.

**NX:** The regional lymph nodes cannot be evaluated

**N0 (N plus zero):**

The cancer has not spread to the regional lymph nodes

**N1:** The cancer has spread to regional lymph nodes

**Distant metastasis.** The 'M' in the TNM system indicates whether the cancer has spread to other parts of the body.



**M0 (M plus zero):**

The cancer has not spread to other parts of the body

**M1:** The cancer has spread to other parts of the body beyond the nearby organs

**Cancer Stage Grouping**

Doctors assign the stage of the cancer by combining the T, N, and M classifications.

**Stage I:**

The tumour is 5 cm or less and has not grown beyond the adrenal gland or spread to regional lymph nodes or other parts of the body (T1, N0, M0)

**Stage II:**

The tumour is larger than 5 cm. It has not grown beyond the adrenal gland or spread to regional lymph nodes or other parts of the body (T2, N0, M0)

**Stage III:**

The tumour is described by the following:

- It is 5 cm or smaller and has spread to the regional lymph nodes but not to other parts of the body (T1, N1, M0)
- It is larger than 5 cm and has spread to the regional lymph nodes but not to other parts of the body (T2, N1, M0)
- It is any size and has grown beyond the adrenal gland but not to nearby organs (T3, N0, M0)

**Stage IV:**

The tumour is described by the following:

- It is any size and has grown into the area around the adrenal gland but not to nearby organs. The tumour has spread to regional lymph nodes but not to other parts of the body (T3, N1, M0)
- It is any size and has spread to nearby organs but not to the lymph nodes or other parts of the body beyond the nearby organs (T4, N0, M0)
- It is any size and has spread to nearby organs. The tumour has spread to the regional lymph nodes but not to other parts of the body beyond the nearby organs (T4, N1, M0)
- The tumour has spread to other parts of the body (any T, any N, M1)

**Recurrent**

Recurrent cancer is cancer that comes back after treatment. If there is a recurrence, the cancer may need to be staged again (called re-staging) using the system above.

(Cancer.Net).

**Treatment of Adrenal Gland Cancer**

Different types of treatments are available for patients with adrenocortical carcinoma. Some treatments are standard (the currently used treatment), while some are being tested in clinical trials. A treatment clinical trial is a research study meant to help improve current treatments or obtain information on new treatments for patients with cancer. When clinical trials show that a new treatment is better than the standard treatment, the new treatment

may become the standard treatment. Patients may want to think about taking part in a clinical trial. Some clinical trials are open only to patients who have not started treatment.

Three types of standard treatment are used:

Surgery - surgery to remove the adrenal gland (adrenalectomy) is often used to treat adrenocortical carcinoma. Sometimes surgery is done to remove the nearby lymph nodes and other tissue where the cancer has spread.

Radiation therapy - radiation therapy is a cancer treatment that uses high-energy x-rays or other types of radiation to kill cancer cells or keep them from growing. There are two types of radiation therapy. External radiation therapy uses a machine outside the body to send radiation toward the cancer. Internal radiation therapy uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer. The way the radiation therapy is given depends on the type and stage of the cancer being treated.

Chemotherapy - chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the cerebrospinal fluid, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). Combination chemotherapy is treatment using more than one anticancer drug. The way the chemotherapy is given depends on the type and stage of the cancer being treated.

New types of treatment that are being tested include:

- Biologic therapy - biologic therapy is a treatment that uses the patient's immune system to fight cancer. Substances made by the body or made in a laboratory are used to boost, direct, or restore the body's natural defences against cancer. This type of cancer treatment is also called biotherapy or immunotherapy.

The effectiveness of immunotherapy as a treatment for an adrenal gland tumour is being researched in clinical trials.

- Targeted therapy - is a type of treatment that uses drugs or other substances to identify and attack specific cancer cells without harming normal cells.

(National Cancer Institute; 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:

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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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