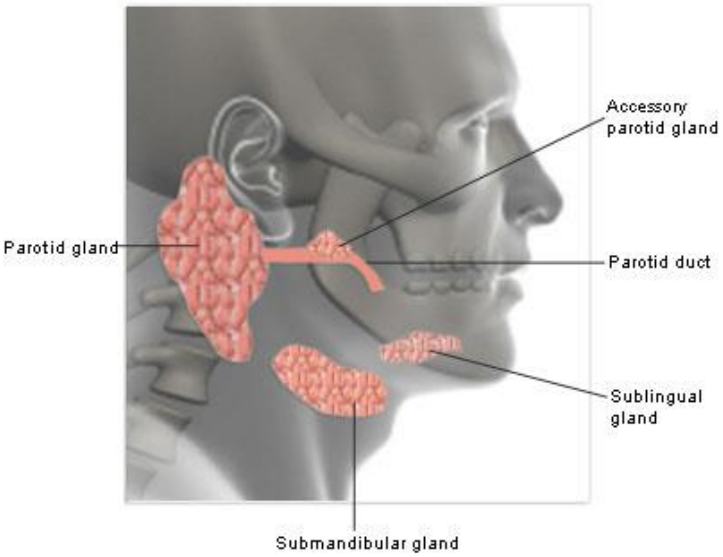
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Salivary Gland Cancer

Introduction

The salivary glands in mammals are exocrine glands, glands with ducts, that produce saliva. They also secrete amylase, an enzyme that breaks down starch into maltose. The gland is internally divided into lobules. Blood vessels and nerves enter the glands at the hilum and gradually branch out into the lobules.



[Picture Credit: Salivary Glands]

The salivary glands consist of:

Parotid glands - the parotid gland is a salivary gland wrapped around the mandibular ramus in humans. It is one of a pair being the largest of the salivary glands, It secretes saliva through Stensen's ducts into the oral cavity, to facilitate mastication and swallowing and to begin the digestion of starches. The secretion produced is mainly serous in nature and enters the oral cavity via the Stensen's duct. It is located posterior to the mandibular ramus and in front of the mastoid process of temporal bone. This gland is clinically relevant in dissections of facial nerve branches while exposing the different lobes of it since any iatrogenic lesion will result in either loss of action or strength of muscles involved in facial expression.

Submandibular glands - the submandibular glands are a pair of glands located beneath the lower jaws, superior to the digastric muscles. The secretion produced is a mixture of both serous fluid and mucus and enters the oral cavity via Wharton's ducts. Approximately 70% of saliva in the oral cavity is produced by the submandibular glands, even though these are much smaller than the parotid glands. One can usually feel this gland, as it is in the upper neck and feels like a rounded ball. It is located about two fingers above the Adam's apple (on a man) and about two inches apart under the chin.

Sublingual glands - the sublingual glands are a pair of glands located beneath the tongue, anterior to the submandibular glands. The secretion produced is mainly mucus in nature, however it is categorized as a mixed gland. Unlike the other two major glands, the ductal

system of the sublingual glands do not have striated ducts and exit from 8-20 excretory ducts. Approximately 5% of saliva entering the oral cavity come from these glands.

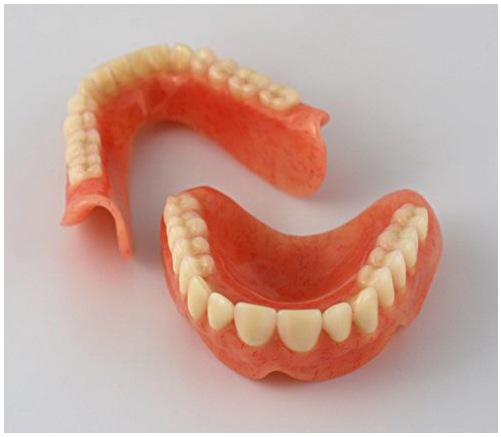
Minor salivary glands - there are 800 - 1000 minor salivary glands located throughout the oral cavity within the submucosa of the oral mucosa in the tissue of the buccal, labial, as well as lingual mucosa, the soft palate, the lateral parts of the hard palate and the floor of the mouth. These are 1-2mm in diameter and unlike the other salivary glands, are not encapsulated by connective tissue, only surrounded by it. The gland is usually a number of acini connected in a tiny lobule. A minor salivary gland may have a common excretory duct with another gland, or may have its own excretory duct. The secretion of the gland is mainly mucous in nature (except for Von Ebner's glands) and have many functions such as coating the oral cavity with saliva. Problems with dentures are sometimes associated with minor salivary glands. The minor salivary glands are innervated by the seventh cranial or facial nerve.

Von Ebner's glands - Von Ebner's glands are glands found in circumvallate papillae of the tongue. It secretes a serous fluid that begin lipid hydrolysis and facilitates the perception of taste (Wikipedia).

Saliva and Dentures

Saliva is critical for retention of, and comfort in, wearing removable prostheses. In the denture wearing population, salivary wetting mechanics are necessary to create adhesion, cohesion and surface tension that ultimately lead to increased retention of prostheses. An intimate fit of denture bases to supporting tissues and the presence of adequate border seals will provide optimal denture function, provided that saliva is adequate in amount, flow and consistency. Saliva allows for the formation of a vacuum pressure on the seating of dentures and contributes significantly to denture retention and the wearer's satisfaction with the prosthesis.

Dentures can dislodge during function and the presence of adequate saliva and swallowing allows for repeated seating of the prosthesis and subsequent retention and denture stabilisation. Adhesion, cohesion and surface tension are interrelated, and they all depend on saliva (Guident).



[Picture Credit: Dentures]

Salivary Gland Cancer

Salivary gland cancer is a rare form of cancer that begins in the salivary glands. Salivary gland cancer can begin in any of the salivary glands in the mouth, neck or throat. It is uncontrolled division and growth of cells within the salivary glands.

- Signs of salivary gland cancer include a lump or trouble swallowing.
- Tests that examine the head, neck, and the inside of the mouth are used to detect (find) and diagnose salivary gland cancer.
- Certain factors affect treatment options and prognosis (chance of recovery).

(Mayo Clinic; National Cancer Institute).

Incidence of Salivary Gland Cancer in South Africa

According to the National Cancer Registry (2012) the following number of salivary gland 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	134	1:1 238	0,36%
Asian males	0	-	-
Black males	67	1:1 672	0,57%
Coloured males	16	1:1 131	0,37%
White males	50	1:658	0,25%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	74	1:3 667	0,20%
Asian females	2	1:4 207	0,19%
Black females	57	1:3 540	0,34%
Coloured females	3	1:18 293	0,07%
White females	13	1:3 279	0,08%

The frequency of histologically diagnosed cases of salivary gland 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	6	3	13	15	24	29	32	10
Asian males	0	0	0	0	0	0	0	0
Black males	2	2	8	10	18	9	11	2
Coloured males	1	0	3	0	2	3	6	0
White males	0	1	2	3	4	16	14	6

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	6	7	8	8	21	11	5	7
Asian females	0	0	1	0	1	0	0	0
Black females	5	5	5	7	19	6	2	4
Coloured females	0	1	1	0	0	0	1	0
White females	0	0	0	1	1	5	2	3

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 Salivary Gland Cancer

Salivary gland cancer may not cause any symptoms. It is sometimes found during a regular dental check-up or physical examination. Symptoms caused by salivary gland cancer also may be caused by other conditions.

A doctor should be consulted if any of the following problems occur:

- a lump (usually painless) in the area of the ear, cheek, jaw, lip, or inside the mouth
- fluid draining from the ear
- trouble swallowing
- numbness in any part of the face
- muscle weakness on one side of the face

- pain in the face that does not go away
- persistent pain in the area of a salivary gland
- trouble opening the mouth widely (Mayo Clinic; Medicine.Net).

Risk Factors

Anything that increases the chance of getting a disease is called a risk factor. Having a risk factor does not mean that you will get cancer; not having risk factors doesn't mean that you will not get cancer. Talk with your doctor if you think you may be at risk. Although the cause of most salivary gland cancers is not known, risk factors include the following:

- Older age.
- Treatment with radiation therapy to the head and neck.
- Being exposed to certain substances at work.

(National Cancer Institute)

Diagnosis of Salivary Gland Cancer

The following procedures may be used in the diagnosis of salivary gland cancer:

Physical examination and history - an examination of the body to check general signs of health. The head, neck, mouth, and throat will be checked for signs of disease, such as lumps or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments will also be taken.

Magnetic resonance imaging (MRI) - a procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of areas inside the body. This procedure is also called nuclear magnetic resonance imaging (NMRI).

Computerised Axial Tomography (CAT) scan - a procedure that makes a series of detailed pictures of areas inside the body, taken from different angles. The pictures are made by a computer linked to an x-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly.

Positron emission tomography scan (PET) - a procedure to find malignant tumour cells in the body. A small amount of radioactive glucose (sugar) is injected into a vein. The PET scanner rotates around the body and makes a picture of where glucose is being used in the body. Malignant tumour cells show up brighter in the picture because they are more active and take up more glucose than normal cells do.

Ultrasound examination - a procedure in which high-energy sound waves (ultrasound) are bounced off internal tissues or organs and make echoes. The echoes form a picture of body tissues called a sonogram. The picture can be printed to be looked at later.

Endoscopy - a procedure to look at organs and tissues inside the body to check for abnormal areas. For salivary gland cancer, an endoscope is inserted into the mouth to look at the mouth, throat, and larynx. An endoscope is a thin, tube-like instrument with a light and a lens for viewing.

Biopsy - the removal of cells or tissues so they can be viewed under a microscope by a pathologist to check for signs of cancer.

- Fine needle aspiration (FNA) biopsy : The removal of tissue or fluid using a thin needle. An FNA is the most common type of biopsy used for salivary gland cancer.

- incisional biopsy : The removal of part of a lump or a sample of tissue that doesn't look normal.
- surgery : If cancer cannot be diagnosed from the sample of tissue removed during an FNA biopsy or an incisional biopsy, the mass may be removed and checked for signs of cancer.

Because salivary gland cancer can be hard to diagnose biopsy samples should be checked by a pathologist who has experience in diagnosing salivary gland cancer.
(Medicine.Net; American Cancer Society).

Factors Affecting Treatment Options and Recovery
The treatment options and prognosis (chance of recovery) depend on the following:

- The stage of the cancer (especially the size of the tumor).
- The type of salivary gland the cancer is in.
- The type of cancer cells (how they look under a microscope).
- The patient's age and general health.

(National Cancer Institute).

Staging of Salivary Gland Cancer
Staging is a way of describing where the cancer 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 cancer'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 cancer.

[Picture Credit: Stages of Salivary Gland 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 and if 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 five stages: stage 0 (zero) and stages I through IV (one through four). 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 metastasised to other parts of the body? **(Metastasis, M)**

T - Tumour

TX primary tumour cannot be assessed
T0 no evidence of primary tumour
T1 tumour 2cm or less in greatest dimenstion without extraparenchymal extension
T2 tumour more than 2cm but not more than 4cm in greatest dimension without extraparenchymal extension
T3 tumour more than 4cm and/or tumour with extraparencymal extension
T4a tumour invades skin, mandible, ear canal or facial nerve
T4b tumour invades base of skull, pterygoid plates or encases carotid artery

N – Regional Lymph Nodes

NX regional lymph nodes cannot be assessed
N0 no regional lymph node metastasis
N1 metastasis in a single ipsilateral lymph node, 3cm or less in greatest dimension
N2 metastasis in a single ipsilateral lymph node, more than 3cm but not more than 6cm in greatest dimensio, or in multiple ipsilateral lymph nodes, none more than 6cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6cm in greatest dimension
N2a metastasis in a single ipsilateral lymph node, more than 3cm but not more than 6cm in greatest dimension
N2b metastasis in multiple ipsilateral lymph nodes, none more than 6cm in greatest dimension
N3 metastasis in a lymph node more than 6cm in greatest dimension

Note: Midline nodes are considered ipsilateral nodes.

M - Distant Metastasis

MX distant metastasis cannot be assessed
M0 no distant metastasis
M1 distant metastasis

pTNM Pathological Classification

The **pT, pN,** and **pM** categories correspond to the **T, N,** and **M** categories**.**

pN0 Histological examination of a selective neck dissection specimen will ordinarily include 6 or more lymph nodes. Histological examination of a radical or modified radical neck dissection specimen will ordinarily include 10 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0. When size is a criterion for pN classification, measurement is made of the metastasis, not of the entire lymph node.

(TNM Classification Help).

Risk Factors for Salivary Gland Cancer

The cause(s) of most salivary gland cancers are unknown, but the following factors may raise a person's risk of developing salivary gland cancer:

Age - two out of every three salivary gland cancers are found in people 55 and older, with an mean age of 64

Radiation exposure - radiation to the head or neck for another medical reason may increase the risk of salivary gland cancer

Radioactive substance exposure - in some reports, exposure to certain radioactive substances has been linked to an increased risk of salivary gland cancer

Environmental/occupational exposure - exposure to sawdust and chemicals used in the leather industry, pesticides, as well as some industrial solvents may increase the risk of some salivary gland cancer that occurs in the nose and sinuses

Other possible risk factors that researchers are investigating but have not proven include exposure to certain metals (nickel alloy dust) or minerals (silica dust), a diet low in vegetables and high in animal fats and exposure to hair dye or hairspray.

There is no known way to prevent salivary gland cancer.
(Cancer.Net)

Treatment of Salivary Gland Cancer
Overview of treatment options:

- There are different types of treatment for patients with salivary gland cancer.
- Patients with salivary gland cancer should have their treatment planned by a team of doctors who are experts in treating head and neck cancer.
- Three types of standard treatment are used:
  - Surgery
  - Radiation therapy
  - Chemotherapy
- New types of treatment are being tested in clinical trials.
  - Radiosensitisers
- Patients may want to think about taking part in a clinical trial.
- Patients can enter clinical trials before, during, or after starting their cancer treatment.
- Follow-up tests may be needed.

Cancer of the salivary glands can often be cured, especially if found early. Although curing the cancer is the primary goal of treatment, preserving the function of the nearby nerves, organs and tissues is also very important.

Descriptions of the most common treatment options for salivary gland cancer are:

Surgery - surgery is performed in nearly all cases of salivary gland cancer and is usually the first treatment. During surgery, a doctor performs an operation to remove the cancerous tumour and some of the healthy tissue around it (called a margin). A surgical oncologist is a doctor who specialises in treating cancer using surgery. The goal of surgery is to remove as much of the tumour as possible and leave negative margins (no trace of cancer in the healthy tissue).

Surgery is typically followed by additional treatment, most often radiation therapy. Sometimes, some people may need more than one operation to remove the cancer and to help restore the appearance and function of the tissues affected.
The type of surgery depends on the location and extent of the tumour:

- Parotidectomy - refers to the removal of the parotid gland. This surgery may involve the facial nerve. If cancer has spread to the facial nerve, frequently a nerve graft is necessary for the person to regain use of some facial muscles. Any tissue that is removed can often be restored by reconstructive surgery and tissue transplantation

- Endoscopic surgery - it is occasionally possible to remove the tumour by endoscopic surgery, which is less destructive to normal tissues than conventional surgery. This is used particularly when a salivary gland tumour begins in the paranasal area (around the nose) or in the larynx. However, this is rare. More often, a tumour may be found unexpectedly during endoscopic surgery for what is believed to be chronic sinusitis (inflammation)

- Neck dissection - a neck dissection is when the surgeon removes lymph nodes in the neck. This may be performed if the doctor suspects that the cancer has spread. A neck dissection may cause numbness of the ear, weakness when raising the arm above the head and weakness of the lower lip. These side effects are caused by injury to nerves in the area. Depending on the type of neck dissection, weakness of the lower lip and arm may go away in a few months. Weakness will be permanent if a nerve is removed as part of the dissection

- Reconstructive surgery - plastic, cosmetic and reconstructive surgery refers to a variety of operations performed in order to repair or restore body parts to look normal after removal of tissues and nerves to eliminate cancer

Surgery can have significant risks, because the cancer may be close to the eyes, mouth, brain, and important nerves and blood vessels in the area. Surgical side effects can include swelling of the face, mouth, and throat, making it difficult to breathe and swallow. Frequently, a person may receive a temporary tracheostomy (hole in the windpipe) to make breathing easier. Also, facial nerves may also be affected, either temporarily or permanently. Facial disfigurement may need to be addressed using reconstructive plastic surgery. If the maxilla (upper jaw) is removed, prosthodontists (a dentist who specialises in replacing teeth and parts of the jaw) play a large role in the rehabilitation process.

Occasionally, it is not possible to remove salivary gland cancer using surgery. This type of tumour is called inoperable. In these cases, doctors will recommend other treatment options.

Radiation therapy - is the use of high-energy x-rays or other particles to kill cancer cells. The most common type of radiation treatment is called external-beam radiation therapy, which is radiation given from a machine outside the body.

When radiation is given using implants, it is called internal radiation therapy or brachytherapy. Internal radiation therapy involves tiny pellets or rods containing radioactive materials that are surgically implanted in or near the cancer site. A radiation therapy regimen (schedule) usually consists of a specific number of treatments given over a set period of time.

A specific method of external radiation therapy, known as intensity modulated radiation therapy (IMRT), allows for more effective doses of radiation therapy to be delivered while reducing the damage to nearby healthy cells and causing fewer side effects.

For salivary gland tumours, it is most often used in combination with surgery, given either before or after the operation. It may also be given along with chemotherapy. Radiation therapy can also be the main treatment for certain types of tumours or if a person cannot have surgery or decides not to have surgery.

Proton therapy (also called proton beam therapy) may be used in instances when a tumour is located close to structures of the central nervous system (brain and spinal cord). It is a type of external-beam radiation therapy that uses protons rather than x-rays. At high energy, protons can destroy cancer cells.

Before beginning radiation treatment for salivary gland cancer, a person should receive a thorough examination from an oncological dentist (a dentist experienced in treating people with head and neck cancer) since radiation therapy can cause tooth decay.

Side effects from radiation therapy to the head and neck may include redness or skin irritation in the treated area, dry mouth (xerostomia) or thickened saliva from damage to salivary glands, bone pain, nausea, fatigue mouth sores and/or sore throat. There may be dental problems.

Other side effects may include pain or difficulty swallowing; loss of appetite, often due to a change in sense of taste; hearing loss, due to the buildup of fluid in the middle ear; as well as buildup of earwax that dries out because of the radiation therapy's effect on the ear canal.

Radiation therapy may also cause a condition called hypothyroidism in which the thyroid gland (located in the neck) slows down and causes the person to feel tired and sluggish. People who receive radiation therapy to the neck area should have their thyroid gland checked regularly.

Chemotherapy - is the use of drugs to kill cancer cells, usually by stopping the cancer cells' ability to grow and divide. Systemic chemotherapy is delivered through the bloodstream to reach cancer cells throughout the body. A chemotherapy regimen (schedule) usually consists of a specific number of cycles given over a set period of time. A patient may receive one drug at a time or a combination of different drugs at the same time.

Chemotherapy is seldom used in the initial treatment of salivary gland cancer. Combined treatments of chemotherapy with radiation therapy are being studied as part of clinical trials to research the combination's effectiveness. For salivary gland cancer, chemotherapy is most often used in later stage cancer or to treat symptoms to improve a patient's quality of life. Some chemotherapy drugs are available in clinical trials that may treat cancer at an earlier stage.

Chemotherapy side effects can include fatigue; nausea; vomiting; hair loss; dry mouth; loss of appetite, often due to a change in sense of taste; weakened immune system; diarrhoea and/or constipation; and open sores in the mouth. Open sores in the mouth, coupled with a low immunity, can lead to infections (Cancer.Net; National Cancer Institute).

About Clinical Trials
Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials
Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer.

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted
Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different “phase” in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers

can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or “control” interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or

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