Cancer Association of South Africa (CANSA)

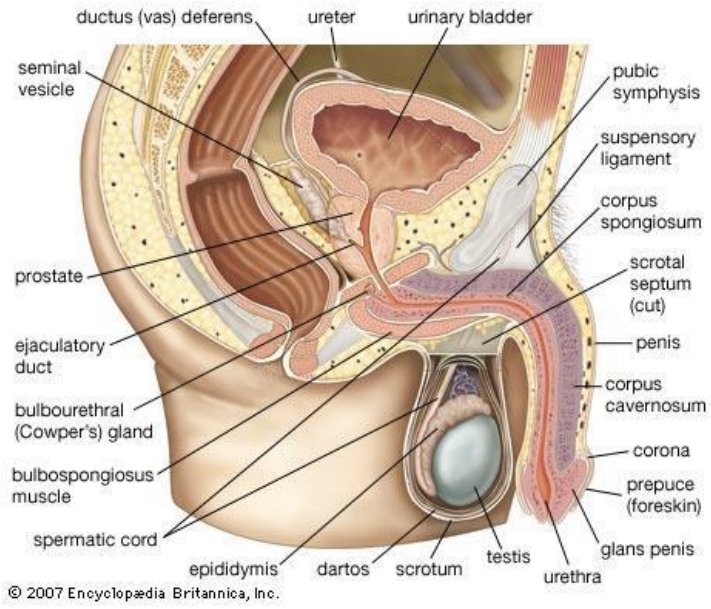
Research • Educate • Support

Fact Sheet
on
Penile cancer

Introduction
The penis is the male sex organ, reaching its full size during puberty. In addition to its sexual function, the penis acts as a conduit for urine to leave the body.

The penis is made of several parts:

- Glans (head) of the penis: In uncircumcised men, the glans is covered with pink, moist tissue called mucosa
- Covering the glans is the foreskin (prepuce). In circumcised men, the foreskin is usually surgically removed and the mucosa on the glans transforms into dry skin



[Picture Credit: Anatomy Male Reproductive System]

- Corpus cavernosum: Two columns of tissue running along the sides of the penis. Blood fills this tissue to cause an erection
- Corpus spongiosum: A column of sponge-like tissue running along the front of the penis and ending at the glans penis; it fills with blood during an erection, keeping the urethra - which runs through it - open
- The urethra runs through the corpus spongiosum, conducting urine out of the body

An erection results from changes in blood flow in the penis. When a man becomes sexually aroused, nerves cause penis blood vessels to expand. More blood flows in and less flows out of the penis, hardening the tissue in the corpus cavernosum

Penile cancer
Penile cancer is cancer that develops within the skin and/or soft tissues of the penis. It is also referred to as cancer of the penis. Penile cancer is one of the rare cancers. If found early, the chances of curing penile cancer are very high.

Penile cancer can develop anywhere on the penis (including the soft tissue) but most commonly develops:

- under the foreskin in men who have not been circumcised
- on the head of the penis (glans penis)

(Cancer Research UK; OncoLink).

Incidence of Penile Cancer in South Africa
According to the National Cancer Registry (2010) the following number of penile cancer cases was histologically diagnosed in South Africa during 2010:

Group 2010	Number of Cases	Lifetime Risk	Percentage of All Cancers
All Males	135	1:1 114	0,50%
Asian males	6	1:795	0,85%
Black males	96	1:1 117	0,90%
Coloured males	11	1:1 281	0,36%
White males	22	1:1 170	0,17%

The frequency of histologically diagnosed cases of penile cancer in South Africa for 2010 was as follows (National Cancer Registry, 2010):

Group 2010	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	0	1	17	25	39	31	13	5
Asian males	0	0	0	2	1	2	0	0
Black males	0	1	15	18	24	18	8	4
Coloured males	0	0	0	3	5	2	1	0
White males	0	0	1	2	7	7	0	1

Risk Factors and Causes of Penile cancer
The following may increase the risk and may contribute to penile cancer:

- Circumcision just after birth, a procedure in which the covering of the tip of the penis is removed, appears to protect men from developing the disease. The risk of penile cancer is about 3 times higher for men who are uncircumcised, or are circumcised later in life.

- Phimosis, or an unretractable foreskin, has also been associated with up to a 10-fold increase in the risk of penile cancer. Possible mechanisms by which circumcision may decrease the incidence of penile cancer include avoiding the development of phimosis and preventing the retention of smegma (skin that has been shed combined with moisture and oil from skin).

- Poor hygiene with chronic retention of smegma.

- Having a sexually transmitted infection (such as HPV virus 16 or 18) may also increase a man's risk of developing penile cancer. Recent scientific advancements have produced human papilloma virus vaccines that may potentially play a role in the prevention of penile cancer, though the area remains controversial. Similar to anal, gynaecologic, and other genital cancers, HPV infection has a strong association with penile cancer. Nearly 50% of patients that develop penile cancer have been found to have the HPV infection. The impact of HPV on prognosis has yet to be determined. In 2009, the FDA approved the use of the HPV vaccine in males aged 9 through 26 years. Although this vaccine is intended to reduce the rate of genital warts, vaccinating prior to initiation of sexual activity may have an effect on penile cancer. The incidence of penile cancer is approximately eight-fold higher in HIV-infected men.

- Having unprotected sexual relations with multiple partners, which increases risk of contracting HPV.

- Smoking – it is thought to damage the DNA of cells in the penis and contribute to the development of penile cancer, especially in men with HPV infection.

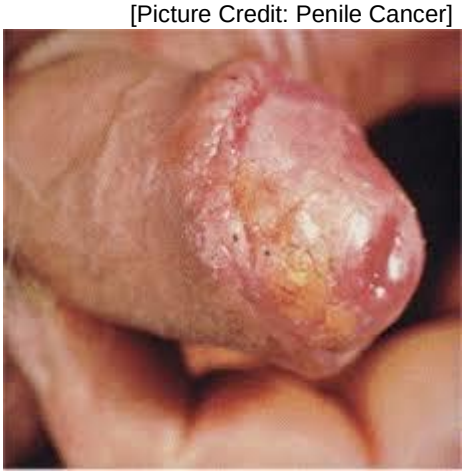
- Psoriasis treatment - men who have been treated for psoriasis with a combination of a drug called psoralen and exposure to ultraviolet light have a higher rate of penile cancer.

(OncoLink; New York Presbyterian Hospital).

Signs and Symptoms of Penile cancer

Often the cancer is only visible when the foreskin is pulled back. Signs and symptoms of penile cancer include:

[Picture Credit: Penile Cancer]



the first sign of penis cancer is often a change in the skin of the penis

- skin thickening – the appearance of a painless nodule or a warty growth specially on the glans penis or foreskin
- change in the colour of the penis
- swelling at the end (glans penis) of the penis
- later signs may include a growth or sore on the penis - especially on the head of the penis (glans) or the foreskin, but also sometimes on the shaft of the penis
- there may be a discharge or bleeding
- Smelly discharge underneath the foreskin
- most penile cancers are painless
- any abnormality of the penis, including warts, blisters, sores, ulcers, white patches, rash, bumps or lumps
- sometimes the cancers appear as flat, bluish-brown growths, or as a red rash, or small crusty bumps

These changes may occur with conditions other than cancer. Penis cancer is easier to treat if it is diagnosed early.

(MacMillan Cancer Support; New York Presbyterian Hospital; WebMD).

Diagnosis of Penile cancer
If the doctor suspects that a patient may have penile cancer, one or more of the following tests may be used to determine the cancer diagnosis and if it has spread. These tests also may be used to find out if treatment is working.

- Biopsy - a biopsy usually is the first test performed to find out if you have penile cancer. The type of procedure depends on the type of tissue or lesion.

- Incisional biopsy - a small part of abnormal tissue is removed. This procedure is used most often for lesions that are larger, ulcerated or that appear to have spread deep into the tissue.

- Excisional biopsy - the whole growth or lesion is removed. Usually, this type of biopsy is performed for small abnormal areas. If the lesion is on the foreskin, the doctor may suggest circumcision.

- Fine needle aspiration (FNA) - this type of biopsy may be used to examine the tissue in lymph nodes. A thin needle is inserted into the groin area. Then cells are drawn out and looked at under a microscope.

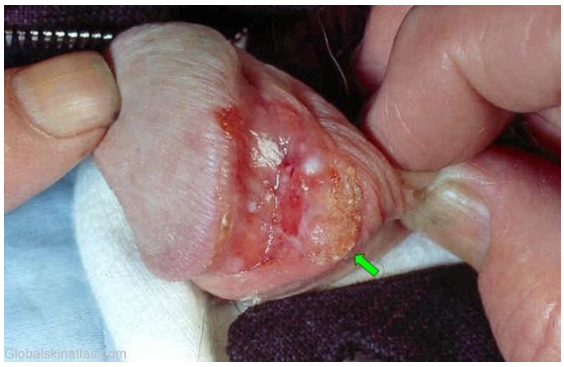
- Imaging tests which may include:

    - CT or CAT (computed axial tomography) scans
    - MRI (magnetic resonance imaging) scans
    - PET (positron emission tomography) scans
    - X-Rays
    - Ultrasound

(MD Anderson Cancer Center; Medscape Reference; Cancer Research UK).

Types of Penile cancer
There are several types of penile cancer, including:

- Epidermoid/squamous cell carcinoma - ninety-five percent (95%) of penile cancer is epidermoid, or squamous cell, carcinoma. This means that the cells look like the tissues that make up skin when looked at with a microscope. Squamous cell carcinoma can begin anywhere on the penis, however, most develop on or under the foreskin. When found at an early stage, epidermoid carcinoma can usually be cured



[Picture Credit: Squamous Cell Carcinoma of Penis]

- Basal cell penile cancer - under the squamous cells in the lower epidermis (one of the layers of the skin tissues that cover the penis) are round cells called basal cells. These can sometimes become cancerous. This is also called non-melanoma skin cancer. Less than 2% of penile cancers are basal cell cancers

- Melanoma - the deepest layer of the epidermis contains scattered cells called melanocytes, which make the melanin that gives skin its colour. Melanoma starts in melanocytes and it is the most serious type of the skin cancer. This cancer sometimes occurs on the surface of the penis

- Adenocarcinoma - adenocarcinoma means that the cancer started in the glandular cells that produce sweat in the skin of the penis. This type is much rarer than squamous cell penile cancer. Only about 5 in 100 penile cancers (5%) are adenocarcinomas

- Sarcoma - about 1% of penile cancers are sarcomas, which are cancers that develop in the tissues that support and connect the body, such as blood vessels, smooth muscle and fat

(Cancer.Net; Cancer Research UK).

Staging of Penile cancer

Once a penile cancer is found, it is necessary to perform more tests to see if the tumour has spread so that appropriate treatment can be recommended. These may involve imaging studies such as CT scans or MRI scans, or procedures such as a cystoscopy.

The extent of the tumour spread is also referred to as the 'stage'. The stage helps guide the doctor's recommendations regarding the optimal treatment for the penile cancer as well as the prognosis.

The staging system for penile cancer is the '**TNM**' system described by the American Joint Committee on Cancer. The '**T'** describes the size or invasiveness of the tumour; the '**N**' describes the spread of the tumour to any glands, or lymph nodes, near the tumour; and the '**M**' describes any distant spread, or metastasis, to other organs or sites of the body. Grade, or how well the tumour cells are organised, is also used in making treatment decisions, but is not included in the official 'TNM' staging system.

The different stages of penile cancer are as follows:

Tumour '**T**'

Tis: carcinoma in situ, or a tumour that involves only the cells in which it began and has not spread to other tissues

Ta: a tumour that has not invaded through the outmost layer of cells, or epithelium, that makes up the skin

T1a: a tumour that has invaded through the epithelium to involve the connective tissue below the skin and is not described by the pathologist as poorly differentiated (how different it appear under the microscope from normal cells)

T1b: a tumour that has invaded through the epithelium to involve the connective tissue below the skin and is determined to be poorly differentiated

T2: a tumour that has invaded through the connective tissues to involve the corpus spongiosum or corpus cavernosum, the deep spongy tissues of the penis

T3: a tumour that has invaded the urethra (the tube that connects the bladder and penis)

T4: a tumour that has invaded other structures such as the bones of the pelvis

Lymph Nodes '**N**'

N0: the cancer has not spread to glands or lymph nodes in the groin or pelvis

N1: the cancer has spread to a single shallow gland or lymph node in the groin, called a superficial inguinal lymph node
N2: the cancer has spread to more than one shallow gland or lymph node in the groin, either or one side or both sides of the groin
N3: the cancer has spread to one or more deep glands or lymph nodes in the groin, called deep inguinal lymph nodes, or has spread to lymph nodes in the pelvis (such as internal iliac or hypogastric lymph nodes, external iliac lymph nodes, or obturator lymph nodes)

Metastasis '**M**' (Spread to other parts)
M0: the cancer has not spread to distant organs or sites of the body
M1: the cancer has spread to distant organs or sites of the body

The overall stage of the tumour (Stage I, II, III, or IV) is then based on a combination of the T, N, and M categories:

Stage 0:	Tis, N0, M0 and Ta, N0, M0
Stage I:	T1a, N0-1, M0
Stage II:	T1a, T2, or T3, N0, M0
Stage IIIa:	T1-3, N1, M0
Stage IIIb:	T1-3, N2, M0
Stage IV:	T4, N0-3, M0 or T1-4, N3, M0, or T1-4, N0-3, M1

A tumour may also be described as recurrent. This means that the tumour has come back after it was originally treated. It may return to the site where it first started or to other areas of the body.
(OncoLink).

Treatment of Penile cancer
When treated in its early stages, penile cancer can be cured in nearly all patients.

Surgery is the most common treatment, particularly for small superficial tumours.

- Mohs surgery - effective approaches to treating squamous cell tumours include Mohs surgery, which enables the surgeon to minimise damage to healthy tissue by progressively removing as little tissue as possible for analysis thereby helping to maintain penile appearance and function.

  Mohs surgery is a surgical procedure to remove a visible lesion on the skin in several steps. First, a thin layer of cancerous tissue is removed. Then, a second thin layer of tissue is removed and viewed under a microscope to check for cancer cells. More layers are removed one at a time until the tissue viewed under a microscope shows no remaining cancer. This type of surgery is used to remove as little normal tissue as possible.

- Cryosurgery - a method using liquid nitrogen to freeze and destroy abnormal cells, and laser surgery - an approach which uses a beam of laser light to vaporize cancer cells, can also be used for squamous and basal cell skin cancer.

- Extensive surgery - more invasive cancers may require extensive surgery, including removal of part of or the entire penis. Extensive surgery to remove the lymph nodes that are toward the penis is often necessary. This is one of the rare circumstances in which metastatic cancer can be cured by surgery alone.

- Radiation therapy – radiation therapy may be recommended as an alternative to surgery for treatment of penile cancer and may help avoid partial or complete removal of the penis. Radiation therapy may be used to target affected lymph nodes in the groin and pelvic area or used following surgery to reduce the risk of the cancer recurring.

- Chemotherapy – chemotherapy may be used topically, which means the medication is placed directly on the skin, or systemically, with drugs given by injection or mouth. Topical chemotherapy reaches cancer. Fluorouracil cream, a chemotherapy drug put on the skin of the penis, is sometimes used for small superficial cancers of the penis.

- Penectomy - the surgical removal of part or all of the penis is the most common and effective procedure to treat penile cancer that has grown into the inside of the penis. A partial penectomy is usually performed when the cancerous tissue and 2 cm margin of healthy tissue can be removed while leaving enough length of the penis for the patient to urinate naturally. When this is not possible, a total penectomy is performed, which is the removal of the entire penis. The surgeon will tunnel the urinary tract underneath the scrotum, requiring the patient to urinate in a sitting position.

- Lymph node dissection - removal of the lymph nodes in the groin and/or pelvis is often performed to determine the stage to treat penile cancer. Removing the lymph nodes when the cancer has spread to the lymph nodes but not anywhere else can get rid of the cancer. However, when the lymph nodes in both the groin and the pelvis are removed on the same side of the body, there is often severe swelling in the leg, called lymphoedema on that side of the body. This can cause discomfort and infections that often come back. Please refer to CANSA's Fact Sheet on Lymphoedema for additional information.
  (MacMillan Cancer Support; tc-cancer.com; University of Chicago Medicine; Fox Chase Cancer Center; Cancer.Net).

Life Changes after Surgery of the Penis

Partially or completely removing the penis is often the most effective way to cure penile cancer, but for many men this cure seems worse than the disease.

It is natural for a man facing treatment for penile cancer to suffer mental distress, depression and feelings of grief or despair. The better one can anticipate and prepare for these feelings in advance, the better the quality of life will be following treatment. Seek referral to a counselor, who can help sort through feelings to adjust to a 'new' body.

Effects on urination - most men are still continent after surgery - that is, they can still control the start and stop of urine flow. In certain cases, a partial penectomy leaves enough of the penis to allow relatively normal urination. Many men who have undergone a total penectomy must sit to urinate.

Effects on sexuality - if penile cancer is diagnosed early, treatments other than penectomy can often be used. Conservative techniques (such as topical chemotherapy, Mohs surgery, and laser surgery) may have little effect on sexual pleasure and intercourse once a patient has fully recovered.

Removing all or part of the penis can have a devastating effect on a man's self-image and ability to have sexual intercourse. Sexual partners may wish to consider counseling to help understand the impact of treatment for penile cancer and to explore other approaches to sexual satisfaction.

[Picture Credit: Penectomy]

Satisfying intercourse is possible for many, but not all men after partial penectomy. The remaining shaft of the penis still becomes erect with arousal. It usually gains enough length to achieve penetration. Although the most sensitive area of the penis (the glans, or 'head') is gone, a man can still reach orgasm and ejaculate normally. His partner should also still be able to enjoy intercourse and often reach orgasm.

Normal intercourse is not possible after total penectomy. Some men give up sex after the surgery. Since penile cancer is most common in elderly men, some may already be unable to have intercourse because of other health problems. If a man is willing to put some effort into his sex life, however, pleasure is possible after total penectomy. He can learn to reach orgasm when sensitive areas such as the scrotum, skin behind the scrotum (perineum) as well as the area surrounding the surgical scars are caressed. Having a sexual fantasy or looking at erotic pictures or stories can also increase excitement.

A man can help his partner reach orgasm by caressing the genitals, by oral sex, or by stimulation with a sexual aid such as a vibrator. The activity some couples enjoy after total penectomy can give hope to those coping with fewer changes in their sex lives.

After total penectomy, surgical reconstruction of the penis may be possible in some cases (American Cancer Society).

Sexual problems after cancer treatment are often caused by changes to the body - from surgery, chemotherapy, or radiation, or by the effects of certain medicines. Sometimes emotional issues can be the cause of sexual problems. Some examples include anxiety, depression, feelings of guilt about how one got cancer, changes in body image after surgery and stress between oneself and a partner.

Worrying about intimacy after treatment - some individuals may struggle with their body image after treatment. Even thinking about being seen without clothes may be stressful. People may worry that having sex will hurt or that they won't be able to perform or will feel less attractive. Pain, loss of interest, depression, or cancer medicines can also affect sex drive.

Some men can no longer get or keep an erection after treatment for penile cancer. Some treatments can also weaken a man's orgasm. Medicine, assistive devices, counseling, surgery, or other approaches may help.

Losing the ability to have children - some cancer treatments can make it impossible for cancer survivors to have children.

Seeing a sex therapist – a sex therapist may be able to help - talk openly about problems, work through concerns and come up with new ways to help.

Focus on the positive. Try to be aware of your thoughts, since they can affect your sex life. Kiss, hug, and cuddle, even if one cannot have the kind of sex that you used to have.

Dating - if single, body changes and concerns about sex can affect how one feels about dating. As one struggles to accept the changes, one may also worry about how someone else will react to physical things, such as scars and possible absence of a penis. One may also find it awkward to bring up sexual problems or loss of fertility, which can make feeling close even harder.

One may wonder how and when to tell a new person in one's life about the cancer and body changes. Here are some ideas that can make it easier to get back into social situations:

- focus on activities that one previously enjoyed, such as taking a class or joining a club
- try not to let cancer be an excuse for not dating or trying to meet people
- wait until there is a sense of trust and friendship before telling a new date about the cancer.
- Practice what to say to someone if worried about how one will handle it. Think about how he or she might react, and be ready with a response.
- think about dating as a learning process with the goal of having a social life to enjoy. Not every date has to be perfect.
- If rejected by some people (which can happen with or without cancer), it does not mean failure - try to remember that not all dates worked out before cancer entered the picture.

Support groups can have many benefits. Even though a lot of people receive support from friends and family, the number one reason they join a support group is to be with others who have had similar cancer experiences. Research shows that joining a support group improves quality of life and enhances survival.

Support groups can:

- give one a chance to talk about your feelings and work through them
- help one deal with practical problems, such as problems at work or school
- help one cope with side effects of treatment.
  (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 his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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