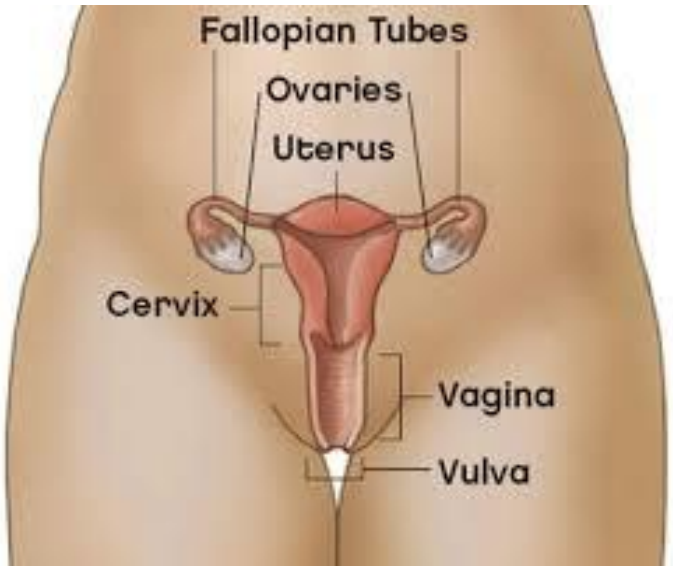
# Cancer Association of South Africa (CANSA)

Research • Educate • Support

## Fact Sheet on Cancer of the Vulva

### Introduction

The vulva (from the Latin *vulva*, plural *vulvae*) consists of the external genital organs of the female.




[Picture Credit: Vulva]

The vulva has many major and minor anatomical structures, including the labia majora, mons pubis, labia minora, clitoris, bulb of vestibule, vulval vestibule, greater and lesser vestibular glands, as well as the opening of the vagina. Its development occurs during several phases, chiefly during the fetal and pubertal periods of time. As the outer portal of the human uterus or womb, it protects its opening by a 'double door': the labia majora (large lips) and the labia minora (small lips). The vagina is a self-cleaning organ, sustaining healthy microbial flora that flow from the inside out; the vulva needs only simple washing to assure good vulvovaginal health, without recourse to any internal cleansing.

The vulva has a sexual function - these external organs are richly innervated and provide pleasure when stimulated. The vulva also contains the opening of the female urethra, but apart from this has little relevance to the function of urination (Wikipedia].

### Cancer of the Vulva

Cancer is a disease in which cells in the body grow out of control. Cancer is always named for the part of the body where it starts, even if it spreads to other body parts later. Cancer of the vulva is a malignant (cancerous) invasive growth in the vulva and mainly affects women later in life.

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## Incidence of Cancer of the Vulva in South Africa

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

| Group - Females 2012 | Actual No of Cases | Estimated Lifetime Risk | Percentage of All Cancers |
|---|---|---|---|
| All females | 323 | 1:782 | 0,86% |
| Asian females | 6 | 1:1 427 | 0,56% |
| Black females | 222 | 1:854 | 1,34% |
| Coloured females | 32 | 1:737 | 0,78% |
| White females | 63 | 1:654 | 0,40% |

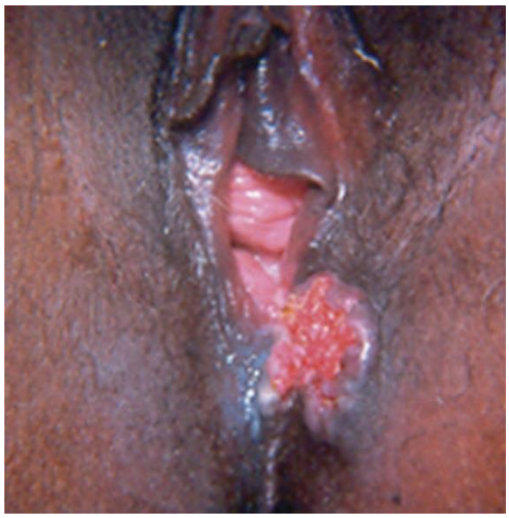
The frequency of histologically diagnosed cases of cancer of the vulva in South Africa for 2012 was as follows (National Cancer Registry, 2012):

| 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 | 1 | 12 | 76 | 79 | 67 | 40 | 27 | 15 |
| Asian females | 0 | 0 | 0 | 1 | 4 | 0 | 1 | 0 |
| Black females | 1 | 10 | 35 | 63 | 38 | 18 | 11 | 3 |
| Coloured females | 0 | 2 | 5 | 7 | 9 | 6 | 0 | 2 |
| White females | 0 | 0 | 1 | 7 | 16 | 14 | 15 | 9 |

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.

## Causes and Risk Factors for Cancer of the Vulva

Several risk factors for cancer of the vulva have been identified. Researchers have made a lot of progress in understanding how certain changes in DNA can cause normal cells to become cancerous. DNA is the chemical that carries the instructions for nearly everything the body's cells do.



Certain genes that promote cell division are called *oncogenes*. Others that slow down cell division or cause cells to die at the right time are called *tumour suppressor genes*. Cancers can be caused by DNA mutations (defects) that turn on oncogenes or turn off tumour suppressor genes. Usually DNA mutations related to cancers of the vulva occur during life rather than having been inherited before birth. Acquired mutations may result from cancer-causing chemicals in tobacco smoke. Sometimes they occur for no apparent reason.

[Picture Credit: Cancer of Vulva]

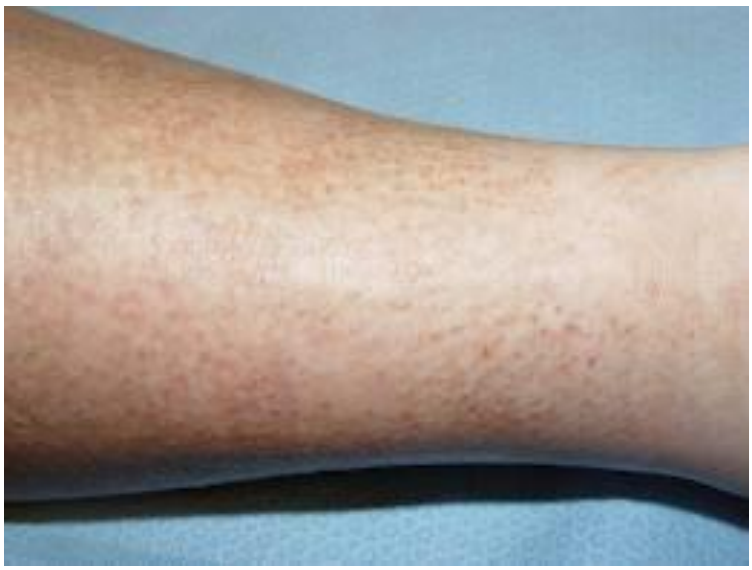
Studies suggest that squamous cell cancer of the vulva (the most common type) can develop in at least 2 ways. In up to half of cases, human papilloma virus (HPV) infection appears to have an important role. Vulvar cancers associated with HPV infection (the basaloid and warty subtypes) seem to have certain distinctive features. They are often found along with several other areas of vulvar intraepithelial neoplasia (VIN). The women who have these cancers tend to be younger and are often smokers.

The second process by which vulvar cancers develop does not involve HPV infection. Vulvar cancers not linked to HPV infection (the keratinising subtype) are usually diagnosed in older women (over age 55). These women may have lichen sclerosus and may rarely have the differentiated type of VIN. DNA tests from vulvar cancers in older women rarely show HPV infection, but often show mutations of the p53 tumour suppressor gene. The p53 gene is important in preventing cells from becoming cancerous. When this gene has undergone mutation, it is easier for cancer to develop. Younger vulvar cancer patients with HPV infection rarely have p53 mutations.

These discoveries have not yet affected treatment. But they may help in finding ways to prevent cancer of the vulva and at some point might lead to changes in treatment. Because vulvar melanomas and adenocarcinomas are so rare, much less is known about how they develop.
(American Cancer Society).

**Lichen Sclerosus**
Lichen sclerosus appears in:

- women (often after menopause)
- men (uncommon)
- children (rare)



[Picture Credit: Lichen Sclerosus]

Early in the disease, small white spots appear on the skin. The spots are usually shiny and smooth. Later, the spots grow into bigger patches. The skin on the patches becomes thin and crinkled. Then the skin tears easily, and bright red or purple bruises are common. Sometimes, the skin becomes scarred. If the disease is a mild case, there may be no symptoms.

Other symptoms are:

- itching (very common)
- discomfort or pain
- bleeding
- blisters

Doctors do not know the exact cause of lichen sclerosus. Some doctors think a too active immune system and hormone problems may play a role. It is also thought that people inherit the likelihood of getting the disease. Sometimes, lichen sclerosus appears on skin that has been damaged or scarred from some other previous injury. Lichen sclerosus is not contagious (it can't be caught from another person).

Women with severe lichen sclerosus in the genitals may not be able to have sex. The disease can cause scars that narrow the vagina. Also, sex can hurt and cause the patches

to bleed. However, treatment with creams or ointments can help. Women with severe scarring in the vagina may need surgery, but only after lichen sclerosus is controlled with medication.

Lichen sclerosus does not cause skin cancer. However, skin that is scarred by lichen sclerosus is more likely to develop skin cancer. If one has the disease, see the doctor every 6 to 12 months. The doctor can look at and treat any changes in the skin.
(National Institute of Arthritis & Musculoskeletal and Skin Diseases).

**Signs and Symptoms of Cancer of the Vulva**
Signs and symptoms of cancer of the vulva may include:

- itching that does not go away
- pain and tenderness
- bleeding that is not from menstruation
- skin changes, such as colour changes or thickening
- a lump, wart-like bumps or an open sore (ulcer)
- abnormal bleeding
- burning
- painful urination
- wart-like growths (similar to genital warts)
- change in the appearance of an existing mole (specific to vulvar melanoma)
- itching
- local pain

(Mayo Clinic; Cancer.Net).

**Diagnosis of Cancer of the Vulva**
If someone suspects that she may have cancer of the vulva she should visit a medical practitioner that specialises in women's cancers (gynaecological cancer specialist).

Apart from a close examination of the vulval area, the doctor will also do a general medical examination of the patient to determine her general condition of health.

The doctor may use a bright light and a magnifier to examine the vulva, so that the skin can be seen more clearly. He/she may then take small samples of tissue (biopsies) from any areas that look unusual. This may be done under a local anaesthetic.

The doctor will also do an internal examination to check the vagina, cervix and the neck of the womb for any abnormality. The doctor will use a speculum (a plastic or metal instrument) to hold the vaginal walls open. He/she may also take a cervical smear test (a small sample of cells taken from the cervix). The doctor may also examine the back passage (anus).

If there is narrowing of the vagina due to lichen sclerosus, or if the vulva is too sore for a full examination, the specialist will arrange to do the examination under general anaesthetic. This is the best way of diagnosing cancer of the vulva and is essential before the cancer is treated. If the vulval area is very painful, the biopsy will also be taken while the patient is under a general anaesthetic.

After the biopsy there may be slight bleeding, which will gradually settle. If the bleeding increases or persists, the doctor should be informed. It will probably take about 7-10 days for the results of the tests to be ready (MacMillan Cancer Support).
A wide spectrum of benign, premalignant, and malignant lesions may involve the vulva. The challenge to the clinician is to differentiate between normal variants, benign findings, and potentially serious disease, which is not always easy.

Conditions to be considered as part of making a differential diagnosis include:

- Paget disease
- melanoma
- Bartholin's gland carcinoma
- basal cell carcinoma of the vulva
- sarcoma of the vulva
- verrucous carcinoma

(Family Practice Notebook).

**Staging of Cancer of the Vulva**
The 2 systems used for staging most types of vulvar cancer, the *FIGO* (International Federation of Gynecology and Obstetrics) system and the American Joint Committee on Cancer TNM staging system, are both very similar. The systems both classify vulvar cancer on the basis of 3 factors: the extent of the tumor (T), whether the cancer has spread to lymph nodes (N) and whether it has spread to distant sites (M). The system described below is the most recent AJCC system, which went into effect January 2010.

The TNM Staging System

**Tumor extent (T)**

**Tis:** the cancer is not growing into the underlying tissues. This stage, also known as *carcinoma in situ*, is not included in the FIGO system.
**T1:** the cancer is growing only in the vulva or perineum
**T1a:** the cancer has grown no more than 1 mm into underlying tissue (stroma) and is 2 cm or smaller in size.
**T1b:** the cancer is either more than 2 cm or it has grown more than 1 mm into underlying tissue (stroma).
**T2:** the tumour can be any size. The cancer is growing into the anus or the lower third of the vagina or urethra (the tube that drains urine from the bladder). This is called stage 2/3 in the FIGO system.
**T3:** the tumour can be any size. The cancer is growing into the upper urethra, bladder or rectum or into the pubic bone. This is called stage 4 in the FIGO system.

**Lymph node spread of cancer (N)**

**N0:** no lymph node spread
**N1:** the cancer has spread to 1 or 2 lymph nodes in the groin with the following features:
**N1a:** the cancer has spread to 1 or 2 lymph nodes and the areas of cancer spread are both less than 5 mm in size

**N1b:** the cancer has spread to one lymph node and the area of cancer spread is 5 mm or greater
**N2:** the cancer has spread to groin lymph nodes with the following features:
**N2a:** the cancer has spread to 3 or more lymph nodes, but each area of spread is less than 5 mm
**N2b:** the cancer has spread to 2 or more lymph nodes with each area of spread 5 mm or greater
**N2c:** the cancer has spread to lymph nodes and has started growing through the outer covering of at least one of the lymph nodes (called extracapsular spread)
**N3:** the cancer has spread to the lymph nodes causing open sores (*ulceration*) or causing the lymph node to be stuck (*fixed*) to the tissue below it

**Distant spread of cancer (M)**

**M0:** no distant spread
**M1:** the cancer has spread to distant sites (includes spread to pelvic lymph nodes)

**Stage Grouping**
The grouping of T, N, and M determines the stage:

**Stage 0 (Tis, N0, M0):**
This is a very early cancer found on the surface of the skin of the vulva only. It is also known as *carcinoma in situ* and as *Bowen disease*. This stage is not included in the FIGO system.

**Stage I (T1, N0, M0):**
The cancer is in the vulva or the perineum (the space between the rectum and the vagina) or both. The tumor has not spread to lymph nodes or distant sites.

**Stage IA (T1a, N0, M0):**
These are stage I cancers with tumours that are 2 cm or less that have grown into the underlying tissue no deeper than 1 mm.

**Stage IB (T1b, N0, M0):**
These are stage I cancers that have invaded deeper than 1 mm and/or are larger than 2 cm.

**Stage II (T2, N0, M0):** The cancer has grown outside the vulva or perineum to the anus or lower third of the vagina or urethra (T2). It has not spread to lymph nodes (N0) or distant sites (M0). In FIGO, this grouping is T2/T3, N0, M0, but it is still stage II.

**Stage IIIA (T1 or T2, N1a or N1b, M0):**
Cancer is found in the vulva or perineum or both (T1) and may be growing into the anus, lower vagina, or lower urethra (T2). Either it has spread to a single nearby lymph node with the area of cancer spread 5 mm or greater in size (N1a); or it has spread to 1 or 2 nearby lymph nodes with both areas of cancer spread less than 5 mm in size (N1b). It has not spread to distant sites (M0). In FIGO, this stage is also called IIIA.

**Stage IIIB (T1 or T2, N2a or N2b, M0):**
Cancer is found in the vulva or perineum or both (T1) and may be growing into the anus, vagina, or lower urethra (T2). Either, the cancer has spread to 3 or more nearby lymph

nodes, with all areas of cancer spread less than 5 mm in size (N2a); or the cancer has spread to 2 or more lymph nodes with each area of spread 5 mm or greater in size (N2b). The cancer has not spread to distant sites (M0). In FIGO, this stage is also called IIIB.

**Stage IIIC (T1 or T2, N2c, M0):**
Cancer is found in the vulva or perineum or both (T1) and may be growing into the anus, lower vagina, or lower urethra (T2). The cancer has spread to nearby lymph nodes and has started growing through the outer covering of at least one of the lymph nodes, called extracapsular spread (N2c). The cancer has not spread to distant sites (M0). In FIGO, this stage is also called IIIC.

**Stage IVA:** Either of the following:
**T1 or T2, N3, M0:**
Cancer is found in the vulva or perineum or both (T1) and may be growing into the anus, vagina, or lower urethra (T2). Cancer spread to nearby lymph nodes has caused it to be stuck (fixed) to the underlying tissue or caused open sores or ulceration (N3). It has not spread to distant sites. In FIGO, this stage is also called IVA.

or

**T3, any N, M0:**
The cancer has spread beyond nearby tissues to the bladder, rectum, pelvic bone, or upper part of the urethra (T3). It may or may not have spread to nearby lymph nodes (any N). It has not spread to distant sites (M0). In FIGO, this stage is also called IVA.

**Stage IVB (any T, any N, M1):**
Cancer has spread to distant organs or lymph nodes (M1). This is the most advanced stage of cancer. In FIGO, this stage is also called IVB.
(American Cancer Society).

<u>The FIGO System</u>
The International Federation of Gynecology and Obstetrics (FIGO) staging systems for vulva, cervix, endometrium, and sarcomas have been revised for the first time in over a decade. The purpose of the staging system is to provide uniform terminology for better communication among health professionals and to provide appropriate prognosis to the patients which results in treatment improvement. This is a constantly evolving process as new therapeutic modalities are developed, new imaging and surgical approaches are applied, and more prognostic information becomes available. The previous system did not reflect the prognosis in some patient subsets where medical research and practice have shown explosive growth of new knowledge in recent years.

The 41$^{st}$ Annual Meeting of the Society of Gynecologic Oncologists was held in March 2010. Several abstracts reported retrospective studies that evaluated the prognostic significance of new 2009 FIGO staging guidelines compared to the old 1988 FIGO system. In endometrial cancer, the reduction in the sub-stages within stage I, and the separation of pelvic and para-aortic nodal involvement further clarified important prognostic factors that yielded clear delineation of survival. The new 2009 FIGO vulvar cancer staging system was validated by clearly demonstrating distinct groups with differing survivals.

***Carcinoma of the Vulva***

IA Tumour confined to the vulva or perineum, ≤ 2cm in size with stromal invasion ≤ 1mm, negative nodes

IB Tumour confined to the vulva or perineum, > 2cm in size or with stromal invasion > 1mm, negative nodes

II Tumour of any size with adjacent spread (1/3 lower urethra, 1/3 lower vagina, anus), negative nodes

IIIA Tumour of any size with positive inguino-femoral lymph nodes
(i) 1 lymph node metastasis greater than or equal to 5 mm
(ii) 1-2 lymph node metastasis(es) of less than 5 mm

IIIB (i) 2 or more lymph nodes metastases greater than or equal to 5 mm
(ii) 3 or more lymph nodes metastases less than 5 mm

IIIC Positive node(s) with extracapsular spread

IVA (i) Tumour invades other regional structures (2/3 upper urethra, 2/3 upper vagina), bladder mucosa, rectal mucosa, or fixed to pelvic bone
(ii) Fixed or ulcerated inguino-femoral lymph nodes

IVB Any distant metastasis including pelvic lymph nodes

(Medscape Today).

**Treatment of Cancer of the Vulva**

Treatment options for cancer of the vulva depend on the type and stage of the cancer, the person's overall health and preferences.

<u>Surgery</u>

Operations used to treat cancer of the vulva include:

- Removing the cancer and a margin of healthy tissue (excision). This procedure, which may also be called a wide local excision or radical excision, involves cutting out the cancer and a small amount of normal tissue that surrounds it. Cutting out what doctors refer to as a margin of normal-looking tissue helps ensure that all of the cancerous cells have been removed.

- Removing a portion of the vulva (partial vulvectomy). During a partial vulvectomy, a portion of the vulva is removed, along with its underlying tissues.

- Removing the entire vulva (radical vulvectomy). Radical vulvectomy involves removal of the entire vulva, including the clitoris and underlying tissues.

- Extensive surgery for advanced cancer. If cancer has spread beyond the vulva and involves nearby organs, the doctor may recommend removing all of the vulva and the involved organs in a procedure called pelvic exenteration. Depending on where the cancer has spread, the surgeon may remove the lower colon, rectum, bladder, cervix, uterus, vagina, ovaries and nearby lymph nodes. If the bladder, rectum or colon is removed, the doctor will create an artificial opening in the body (stoma) for waste to be removed in a bag (ostomy).

- Reconstructive surgery. Treatment of cancer of the vulva often involves removal of some skin from the vulva. The wound or area left behind can usually be closed without grafting skin from another area of the body. However, depending on how widespread the cancer is and how much tissue the doctor needs to remove, he/she

may perform reconstructive surgery — grafting skin from another part of the body to cover this area.

Surgery to remove the entire vulva carries a risk of complications, such as infection and problems with healing around the incision. In addition, with part or all of the vulvar padding gone, it can be uncomfortable to sit for long periods. The genital area may feel numb, and it may not be possible to achieve orgasm during sexual intercourse.

- Surgery to remove nearby lymph nodes. Cancer of the vulva often spreads to the lymph nodes in the groin, so the doctor may remove these lymph nodes at the time of surgery to remove the cancer. Depending on the situation, the doctor may remove only a few lymph nodes or many lymph nodes.

  Removing lymph nodes can cause fluid retention and leg swelling, a condition called lymphoedema.
  Doctors are studying a technique that may allow surgeons to remove fewer lymph nodes. Called sentinel lymph node biopsy, this procedure involves identifying the lymph node where the cancer is most likely to spread first. The surgeon then removes that lymph node for testing. If cancer cells aren't found in that lymph node, then it's unlikely that cancer cells have spread to other lymph nodes.

Radiation therapy

Radiation therapy uses high-powered energy beams, such as X-rays, to kill cancer cells. Radiation therapy for cancer of the vulva is usually administered by a machine that moves around your body and directs radiation to precise points on your skin (external beam radiation).

Radiation therapy is sometimes used to shrink large cancer of the vulvas in order to make it more likely that surgery will be successful. Radiation is sometimes combined with chemotherapy, which can make cancer cells more vulnerable to radiation therapy.
If cancer cells are discovered in your lymph nodes, your doctor may recommend radiation to the area around your lymph nodes to kill any cancer cells that might remain after surgery.

Chemotherapy

Chemotherapy is a drug treatment that uses chemicals to kill cancer cells. Chemotherapy drugs are typically administered through a vein in the arm or by mouth.

For women with advanced cancer of the vulva that has spread to other areas of the body, chemotherapy may be an option. Sometimes chemotherapy is combined with radiation therapy to shrink large cancer of the vulvas in order to make it more likely that surgery will be successful.
(Mayo Clinic; MacMillan Cancer Support).

**Follow-up Tests after Treatment**

After completing cancer of the vulva treatment, the doctor may recommend periodic follow-up exams to look for a cancer recurrence. Even after successful treatment, cancer of the vulva can return. The doctor will determine the correct schedule of follow-up examinations.

Doctors generally recommend examinations two to four times each year for the first two years after cancer of the vulva treatment.

**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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