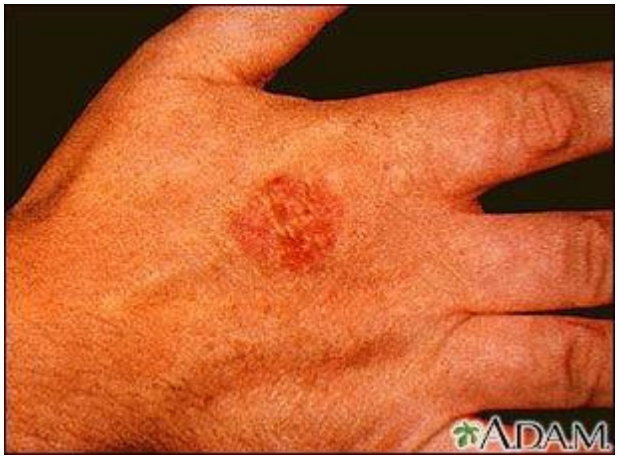
The Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Squamous Cell Carcinoma

Introduction

There are two main categories of skin cancer, namely melanomas and non-melanoma skin cancers. Squamous cell carcinoma is one of the non-melanoma skin cancers (British Skin Foundation). Squamous Cell Carcinoma (SCC) is a type of carcinoma that arises from squamous epithelium. It is the second most common form of skin cancer in South Africa. It is also sometimes referred to as cancroid.



[Picture Credit: Squamous Cell Carcinoma]

SCC tends to develop on skin that has been exposed to the sun for years. It is most frequently seen on sun-exposed areas of the body such as the head, neck and back of the hands. Although women frequently get SCC on their lower legs it is possible to get SCC on any part of the body including the inside of the mouth, lips and genitals. People who use tanning beds have a much higher risk of getting SCC – they also tend to get SCC earlier in life (American Academy of Dermatology).

Incidence of Skin Cancer Among Individuals of Colour

Most skin cancers are associated with ultraviolet (UV) radiation from the sun or tanning beds, and many people of colour are less susceptible to UV damage thanks to the greater amounts of melanin darker skin produces. Melanin is the protective pigment that gives skin and eyes their colour, however, people of colour can still develop skin cancer from UV damage.

Additionally, certain skin cancers are caused by factors other than UV - such as genetics or other environmental influences - and may occur on parts of the body rarely exposed to the sun. For example, darker-skinned people are more susceptible to acral lentiginous melanoma (ALM), an especially virulent form of melanoma (the deadliest type of skin cancer) that typically appears on the palms of the hands and soles of the feet.

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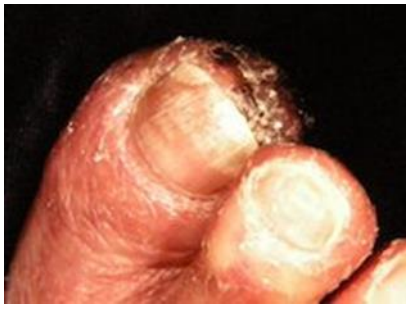
Acral lentiginous melanoma (ALM) accounts for about 5% of melanoma cases, and is a leading cause of skin cancer deaths. The disease initially appears as a bruise or nail streak on the skin. Most patients do not notice ALM until it has already begun to spread aggressively throughout the body. Bob Marley was killed from this form of malignant tumour under his toenail. ALM (also called subungual melanoma) affects people of Asian or African descent more than any other race or ethnicity.



[Picture Credit: Acral Lentiginous Melanoma]

The average patient is between sixty and seventy years of age, but ALM can affect people of any age. This classification of the disease is generally found on the hands, feet and other areas of the body where very little hair grows.

Presently, sunlight is not a proven cause of this condition. When the tumour is deeper than 1.0 mm or has spread to other parts of the body through the lymph nodes, the cancer frequently results in death.

Different ethnicities are at higher risk for particular skin malignancies: Latinos, Chinese, and Japanese Asians tend to develop basal cell carcinoma (BCC), the most common skin cancer. But the second most common, squamous cell carcinoma (SCC), is more frequent among African Americans and Asian Indians.
(Skin Cancer Foundation; DermNet NZ; Know Cancer).

Incidence of Squamous Cell Carcinoma (SCC) in South Africa
According to the National Cancer Registry (2012) the following number of squamous cell carcinoma (SCC) 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	3 847	1:42	10,43%
Asian males	23	1:313	2,73%
Black males	417	1:269	3,58%
Coloured males	353	1:35	8,15%
White males	3 054	1:13	15,23%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	2 612	1:98	6,94%
Asian females	26	1:323	2,40%
Black females	374	1:483	2,27%
Coloured females	242	1:92	5,81%
White females	1 969	1:26	12,41%

The frequency of histologically diagnosed cases of squamous cell carcinoma (SCC) 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	5	10	79	201	511	1 010	1 127	854
Asian males	0	1	0	2	4	7	4	5
Black males	4	6	37	51	86	94	76	47
Coloured males	0	0	8	20	46	103	96	87
White males	1	3	34	127	374	806	951	725

Group - Females 2011	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	4	22	60	136	200	505	723	785
Asian females	1	1	0	1	5	7	3	6
Black females	1	17	49	46	68	50	66	66
Coloured females	1	0	2	17	36	45	63	72
White females	1	4	8	72	221	402	591	640

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.

Symptoms Squamous Cell Carcinoma (SCC)

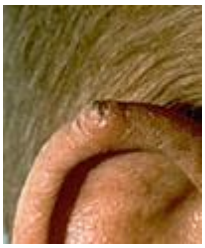
Although squamous cell carcinomas usually develop on sun-exposed skin, it can occur anywhere on the body, including inside the mouth, on the anus, and on the genitals in both men and women. The appearance of the primary tumours can vary, but the most common forms include:

- A firm, red nodule on the face, lower lip, ears, neck, hands or arms, that may bleed sometimes
- A flat lesion with a scaly crust on the face, ears, neck, hands or arms
- A new ulceration or raised area on a pre-existing scar or ulcer
- An ulcer or flat, white patch inside the mouth
- A red, raised patch or ulcerated sore on or in the anus or on the genitals

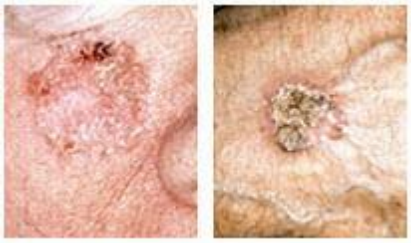
Squamous cell carcinomas are usually slow growing and can be difficult to spot, especially when it appears on skin that has other signs of sun damage, such as changes in pigmentation, loss of elasticity and wrinkling.

It can also be mistaken for actinic keratoses — rough, scaly, dark brown or pink patches that appear after years of sun exposure. A small number of actinic keratoses eventually develop into squamous cell carcinomas (Mayo Clinic).

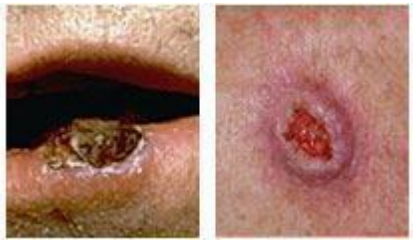
Squamous cell carcinomas typically appear as a persistent thick, rough, scaly patch that can bleed if bumped. They often look like warts and sometimes appear as open sores with a raised border and a crusted surface over an elevated pebbly base.



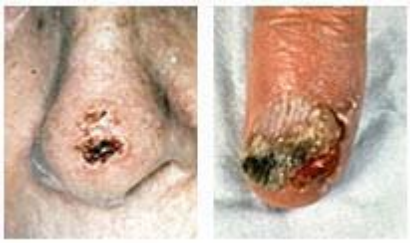
A wart-like growth that crusts and occasionally bleeds



A persistent, scaly red patch with irregular borders that sometimes crusts or bleeds



An elevated growth with a central depression that occasionally bleeds. A growth of this type may rapidly increase in size



An open sore that bleeds and crusts and persists for weeks

(Skin Cancer Foundation; PubMed Health).

Risk Factors for Squamous Cell Carcinoma (SCC)

Anyone who has had SCC has an increased risk for getting another skin cancer. The following are recommended to manage this higher risk:

- Keep all follow-up appointments with a dermatologist – if found early, SCC can be cured
- Perform a skin self-examination – patients who are diagnosed with SCC are to be taught how to examine their skin for signs of skin cancer. Regular (at least once per year) skin self-examinations should be conducted
- Observe the skin for any unnatural growth, bleeding or any changes. Report any changes to a dermatologist

- Protect the skin from the sun – refer to the CANSA Fact Sheet on Solar Radiation and Skin Cancer for information
- Avoid sunbed tanning – sunbed use has been directly linked to the occurrence of skin cancer
- In the case of a history of SCC, it is recommended to use a condom – this will prevent a Human Papilloma Virus (HPV) infection which reduces the risk for getting SCC on the genitals
- Do not use any tobacco products – the use of tobacco products has been directly linked to various cancers including SCC
- Avoid the intake of alcohol. Alcohol was listed has been listed a Group 1 carcinogen by the International Agency for Research in Cancer (IARC). The risk of various types of cancer — including SCC — increases with the amount of alcohol that is consumed as well as the length of time of drinking alcohol regularly
- Precancerous skin conditions - although the majority of actinic keratoses do not become cancerous, squamous cell carcinomas can occasionally arise from these lesions. Leukoplakia and Bowen's disease can also be precursors to SCC
- Exposure to industrial compounds - repeated exposure to radiation, and exposures to coal tar, arsenic or other industrial compounds can raise a person's risk of SCC
- Weakened immune system - people with a weakened immune system are also at an increased risk for developing SCC. Examples would include patients with lymphoma and leukaemia on chemotherapy or who are treated with drugs to prevent organ transplant rejection.
- Age - a long latency period usually occurs between exposure to harmful UV radiation and the development of SCC, putting older people at a greater risk. This risk also grows as people grow older because the body loses its ability to repair DNA damage over time.
- Rare genetic disorder - people with *Xeroderma Pigmentosum*, which causes an extreme sensitivity to sunlight, have a greatly increased risk of developing skin cancer because they have little or no ability to repair skin damaged by ultraviolet light.

(American Academy of Dermatology; Life is Beautiful; Memorial Sloan-Kettering Cancer Centre; Mayo Clinic).

Reducing the Risk for Squamous Cell Carcinoma (SCC)

The following guidelines will assist in the prevention of Squamous Cell Carcinoma:

- Wear protective clothing, including a long-sleeved shirt, long pants, a wide-brimmed hat and sunglasses with at least UV400 protection whenever possible between 10:00 and 15:00 when the sun's rays are at its strongest
- Seek shade when appropriate, especially when the sun's rays are the strongest from 10:00 to 15:00
- Regularly use a broad-spectrum sunscreen. Refer to CANSA's Fact Sheet on Solar Radiation and Skin Cancer for information
- Protect children from the sun by using shade, protective clothing, and applying sunscreen
- Use extra caution near water, cement surfaces and sand which can reflect the sun's rays and increase the chances of sunburn
- Avoid tanning beds.
- Obtain Vitamin D safely through a healthy diet (which may include vitamin D_3 supplements). Don't seek out the sun during 10:00 and 15:00.

(Stanford Cancer Institute; Mayo Clinic; American Academy of Dermatology).

Please refer to CANSA's Fact Sheet on Solar Radiation and Skin Cancer for additional information.

Diagnosis of Squamous Cell Carcinoma

Potential squamous cell carcinomas are first examined visually. The doctor or dermatologist will first examine the area, noting its size, shape, colour and texture, as well as any bleeding or scaling. The doctor may also examine nearby lymph nodes to see if they are enlarged.

A dermatologist may use a special dermascope (e.g. FotoFinder Dermascope), microscope or magnifying lens to examine the suspicious spot more closely, a process called dermatoscopy. He/she may also take a digital or photographic image of any suspicious spots.

The next step in diagnosing squamous cell carcinoma is to remove a piece of the suspicious growth for examination by a laboratory, where the scientist will look for cancerous cells. In many cases, the doctor will remove the whole growth. During this procedure the doctor will numb the area before removing a tissue sample. There are several different biopsy methods, but removal of the entire growth through an excisional biopsy is often sufficient to remove a squamous cell carcinoma. Other types of biopsies include a shave biopsy, in which the doctor shaves off the top layers of the lesion and a punch biopsy where the doctor uses a special tool to cut a tiny round piece of the tumour, including deeper layers of the skin.

Special tests may also be performed to determine whether or not the cancer has spread beyond the skin. Although squamous cell carcinoma does not typically spread, when it does the first place it usually spreads is to nearby lymph nodes. The doctor may feel to see if any lymph nodes are enlarged. He/she may also take a biopsy of any suspicious lymph nodes to see if they contain cancer cells.

In very rare cases where it is suspected that the cancer has spread, other imaging tests, such as x-rays, computed tomography (CT) scans or magnetic resonance imaging (MRI) scans may be used to determine if cancer cells have spread to internal organs and bones. (Cancer Treatment Centers of America).

Staging of Squamous Cell Carcinoma (SCC)

In 2011, the American Joint Committee on Cancer (AJCC) published a new staging systemic for cutaneous SCC for the 7th Edition of the AJCC manual. This evaluates the dimensions of the original primary tumour (T) and its metastases to lymph nodes (N).

Tumour Staging for Cutaneous SCC

TX	The primary tumour cannot be assessed
T0	There is no evidence of a primary tumour
Tis	Carcinoma *in situ*
T1	The tumour is <2cm without high-risk features
T2	The rumour is >2cm The tumour is <2cm with high-risk features
T3	Tumour with invasion of maxilla, mandible, orbit or temporal bone
T4	Tumour with invasion of axial or appendicular skeleton or perineural invasion of skull base

High risk features of the primary tumour include depth >2mm, perineural invasion, location on ear or nonglabrous lip (technical term for an anatomically atypical lack of hair, down, or similar structures. This may be natural or due to loss because of a physical condition, such as *alopecia universalis*, which causes hair to fall out or prevents its growth) and poorly differentiated or undifferentiated tumour on pathology.

Nodal Staging for Cutaneous SCC

NX Regional lymph nodes cannot be assessed
N0 No regional lymph nodes metastasis
N1 Metastasis in one local lymph node <3cm
N2 Metastasis in one local lymph node >3cm
Metastasis in >1 local lymph node <6cm
N3 Metastasis in lymph node >6cm
(DermNet NZ).

Prognosis (Outlook) for Squamous Cell Carcinoma (SCC)
How well a patient does depends on many things, including how quickly the cancer was diagnosed. Most cases of SCC are cured when treated early. Some squamous cell cancers may return.

Patients who have had skin cancer, should have regular check-ups so that a doctor can examine their skin. Patients should also examine their skin once a month. Use a hand mirror to check hard-to-see places. Consult a dermatologist when anything unusual is noticed (Medline Plus).

Treatment of Squamous Cell Carcinoma (SCC)
Most squamous cell skin cancers that are found and treated at an early stage, can be removed or destroyed with local treatment methods. Small squamous cell cancers can usually be cured with these treatments. Larger squamous cell cancers are harder to treat, and the chance of recurrence for fast-growing cancers can be as high as 50% for large, deep tumours. In rare cases, squamous cell cancers may spread to lymph nodes or distant sites. If this happens, further treatment with radiation therapy and/or chemotherapy may be needed. Treatment includes:

Simple excision - Simple excision (cutting out the tumour, along with a small margin of normal skin) is often used to treat squamous cell carcinomas.

Curettage and electrodesiccation - Curettage and electrodesiccation is sometimes useful in treating small squamous cell carcinomas (less than 1 cm across), but it is not recommended for larger tumours.

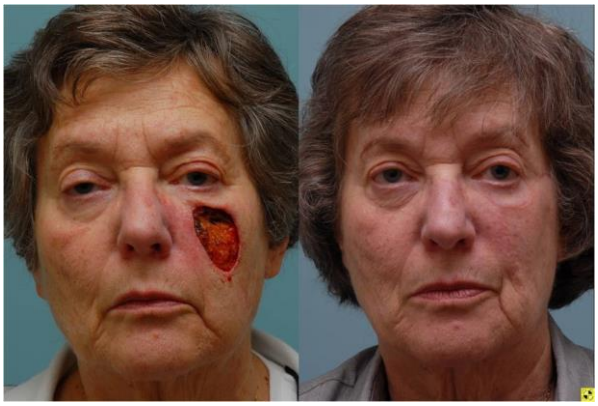
Mohs surgery - Mohs surgery has the highest cure rate. It is especially useful for squamous cell carcinomas larger than 2 cm (about 4/5 inch) across or with poorly defined edges, for tumours that have come back after other treatments, for cancers that are spreading along nerves under the skin, and for cancers on certain areas of the face or genital area

New treatments for skin cancer are appearing and evolving rapidly in recent years. However, one surgical technique has more than stood the test of time. Developed by Dr. Frederick Mohs in the 1930s, Mohs' micrographic surgery has, with a few refinements, come to be embraced over the past decade by an increasing number of surgeons for an ever-widening variety of skin cancers.

Today, Mohs' surgery has come to be accepted as the single most effective technique for removing Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC), the two most common skin cancers. It accomplishes the nifty trick of sparing the greatest amount of healthy tissue while also most completely expunging cancer cells; cure rates for BCC and SCC are an unparalleled 98 percent or higher with Mohs' surgery, significantly better than the rates for standard excision or any other accepted method.

[Picture Credit: Mohs' Surgery 1]

The reason for the technique's success is its simple elegance. Mohs' surgery differs from other techniques in that microscopic examination of all excised tissues occurs during, rather than after the surgery, thereby eliminating the need to 'estimate' how far out or deep the roots of the skin cancer go. This allows the Mohs surgeon to remove all of the cancer cells while sparing as much normal tissue as possible. The procedure entails removing one thin layer of tissue at a time; as each layer is removed, its margins are studied under a microscope for the presence of cancer cells. If the margins are cancer-free, the surgery is ended. If not, more tissue is removed from the margin where the cancer cells were found, and the procedure is repeated until all the margins of the final tissue sample examined are clear of cancer. In this way, Mohs' surgery eliminates the guesswork in skin cancer removal, producing the best therapeutic and cosmetic results.



[Picture Credit: Mohs' Surgery 2]

In the past, Mohs' surgery was rarely chosen for Malignant Melanoma surgery for fear that some microscopic melanoma cells might be missed and end up spreading around the body (metastasising). However, efforts to improve the Mohs surgeon's ability to identify melanoma cells have led to special stains that highlight these cells, making them much easier to see under the microscope. Thus, more Mohs surgeons are now using this procedure with certain melanomas. With the rates for melanoma and other skin cancers continuing to skyrocket, Mohs' surgery will play an ever more important role in the coming decades.
(Skin Cancer Foundation).

Radiation therapy - Radiation therapy is often a good option for patients with large cancers, especially in areas where surgery is difficult (eyelids, ears or nose), or for patients who may not be able to tolerate surgery. It is not used as much as an initial treatment in younger patients because of the possible risk of long-term problems.

Radiation is sometimes used after surgery (simple excision or lymph node dissection) if all of the cancer was not removed (if the surgical margins were positive) or if there is a chance that some cancer may remain. Radiation can also be used to treat cancers that have come back after surgery and have become too large or deep to be removed surgically.

Cryosurgery - Cryosurgery is used for some early squamous cell carcinomas, especially in people who cannot have surgery, but is not recommended for larger invasive tumours or those on certain parts of the nose, ears, eyelids, scalp or legs.

Laser therapy - An intense beam of light vaporises growths, usually with little damage to surrounding tissue and with a reduced risk of bleeding, swelling and scarring. Lasers are often used to treat superficial carcinomas on the lips.

Treating advanced squamous cell cancers

Lymph node dissection: Removing regional (nearby) lymph nodes is recommended for some squamous cell carcinomas that are very large or deeply invasive and in cases where the lymph nodes feel enlarged and/or hard. After the lymph nodes are removed, they are looked at under a microscope to see if they contain cancer cells. In some cases, radiation therapy might be recommended after surgery.

Systemic chemotherapy: Systemic chemotherapy is an option for patients with squamous cell cancer that has spread to lymph nodes or distant organs. In some cases it is combined with surgery or radiation therapy.
(American Cancer Society; PubMed Health; Mayo Clinic)

Complications of Squamous Cell Carcinoma (SCC)

When treated early, squamous cell carcinomas generally cause no problems.

- Untreated squamous cell carcinoma can destroy healthy tissue around the tumour, spread to the lymph nodes or other organs, and may be fatal (although this is uncommon)
- People who have had organ transplants or have chronic lymphocytic leukaemia or HIV/AIDS are far more likely to have an aggressive form of squamous cell carcinoma than are people who are otherwise healthy

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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