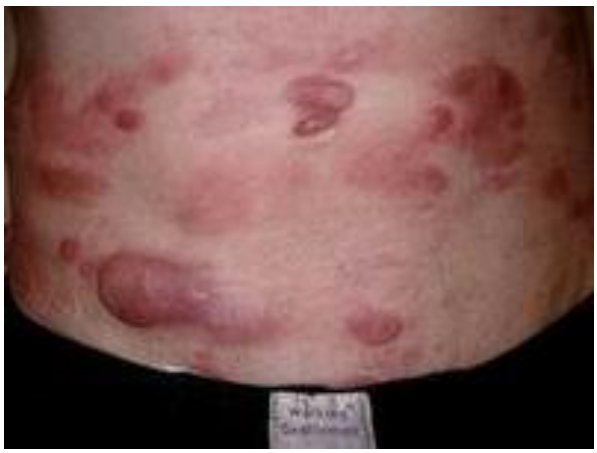
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Mycosis Fungoides

Introduction

Mycosis fungoides, also known as Alibert-Bazin syndrome or granuloma fungoides, is the most common form of cutaneous T-cell lymphoma. It generally affects the skin, but may progress internally over time. Symptoms include rash, tumours, skin lesions, and itchy skin. While the cause remains unclear, most cases are not genetic or hereditary. It occurs mostly in people over 20 years of age, and it is more common in men than women. (Wikipedia).



[Picture Credit: Mycosis Fungoides]

Mycosis Fungoides (MF)

Lymphoma is the most common type of blood cancer. The two main forms of lymphoma are Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumour. The body has two main types of lymphocytes that can develop into lymphomas: B-lymphocytes (B-cells) and T-lymphocytes (T-cells).

T-cell lymphomas account for approximately 15 percent of all NHLs. There are many different forms of T-cell lymphomas, some of which are extremely rare. Most T-cell lymphomas can be classified into two broad categories: aggressive (fast-growing) or indolent (slow-growing). One of the most common forms of T-cell lymphoma is cutaneous T-cell lymphoma (CTCL), a general term for T-cell lymphomas that involve the skin. CTCL also can involve the blood, the lymph nodes, and other internal organs. Symptoms can include dry skin, itching (which can be severe), a red rash, and enlarged lymph nodes. The disease affects men more often than women and usually occurs in men in their 50s and 60s – usually after the age of 20 although children have been diagnosed with the condition. (Lymphoma Research Foundation).

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Early in the course of disease, skin lesions may be non-specific, so confusion with benign (non-cancerous) conditions is common. Over time, mycosis fungoides becomes more aggressive, and in about 20 per cent of patients the disease will undergo a transformation to highly malignant lymphoma with widespread dissemination into various organs of the body. Late-stage disease is associated with the decline of the immune system. Death often results from systemic infection, especially with *Staphylococcus aureus* or *Pseudomonas aeruginosa*, and other organisms.
(European Federation of Pharmaceutical Industries and Associations).

Signs and Symptoms of Mycosis Fungoides (MF)
Mycosis fungoides is the most common form of cutaneous T-cell lymphoma (CTCL). It does not look the same for all patients. This form of CTCL may present itself as patches, plaques or tumours.

Mycosis fungoides - typically presents with flat, red, scaly patches that are often mistaken for eczema, psoriasis or non-specific dermatitis. Plaques are thicker, raised lesions. Tumours are raised bumps, which may or may not ulcerate (break down). A common characteristic is itching, although some patients do not experience itching. It is possible to have one or all three types of presentations.

Common Signs & Symptoms of Mycosis Fungoides

Patches	**Plaques**
Itching	**Skin Ulcers**
Tumours	

Sezary syndrome - is another common form of CTCL, and is considered an advanced, variant of mycosis fungoides, which distinguishes itself by the presence of malignant lymphocytes in the blood.

Sezary syndrome is characterised by diffusely red, scaly, itchy skin (erythroderma) covering over 80 percent of the body. Other skin changes include thickening (hyperkeratosis) of the palms and soles, fragile nails, hair thinning and thickening of the eyelid margins (ectropion). These skin changes are associated with enlarged lymph nodes and the presence of malignant lymphocytes (Sezary cells) circulating in the blood.

Common Signs & Symptoms of Sezary Syndrome

Diffuse Scaling Skin (Erythroderma)	**Thickening of Palms and Soles (Hyperkeratosis)**
Hair Thinning	**Eyelid Margin Thickening (Ectropion)**
Itching	**Enlarged Lymph Nodes**

(Cutaneous Lymphoma Foundation)

Incidence of Mycosis Fungoides (MF) in South Africa

The National Cancer Registry (2012) does not provide any information on the incidence of Mycosis Fungoides.

According to the National Cancer Registry of 2012, the following number of Non-Hodgkin's Lymphoma 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	933	1:206	2,53%
Asian males	29	1:222	3,39%
Black males	555	1:274	4,76%
Coloured males	79	1:212	1,81%
White males	271	1:121	1,35%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	797	1:311	2,12%
Asian females	21	1:333	1,96%
Black females	500	1:401	3,03%
Coloured females	70	1:272	1,68%
White females	206	1:179	1,30%

The frequency of histologically diagnosed cases of Non-Hodgkin's Lymphoma 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	32	46	134	208	199	146	105	49
Asian males	1	0	2	4	7	5	5	2
Black males	24	33	108	158	127	53	22	9
Coloured males	3	5	9	12	18	12	11	6
White males	4	8	12	30	44	74	62	31

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	17	50	144	188	141	106	92	44
Asian females	0	0	2	4	6	3	4	0
Black females	11	39	120	156	81	37	27	10
Coloured females	2	3	8	14	9	13	14	6
White females	4	8	13	12	43	49	47	26

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.

Diagnosis of Mycosis Fungoides (MF)

Mycosis fungoides (MF), the most common cutaneous T-cell lymphoma, is a low-grade cutaneous lymphoma characterised by skin-homing CD4+ T cells. It is notable for highly symptomatic progressive skin lesions, including patches, plaques, tumours, and erytheroderma, and has a poorer prognosis at later stages. Diagnosis remains difficult owing to MF's nonspecific skin presentation and identification of the optimal treatment strategy is challenging given the paucity of controlled trials and numerous and emerging treatment options.

(Galper, *et al*.).

In most cases of mycosis fungoides, the diagnosis is reached owing to its clinical features, disease history, and histomorphologic and cytomorphologic findings. An additional diagnostic criterion to distinguish CTCL from inflammatory dermatoses is demonstration of a dominant T-cell clone in skin biopsy specimens by a molecular assay (i.e., Southern blot, polymerase chain reaction [PCR]). Genetic testing may also be considered.

The following laboratory tests are included in the diagnostic workup of mycosis fungoides:

- Complete blood count with differential; review the buffy coat smear for Sézary cells
- Liver function tests: Look for liver-associated enzyme abnormalities
- Uric acid and lactate dehydrogenase levels: These are markers of bulky and/or biologically aggressive disease
- Flow cytometric study of the blood (include available T-cell–related antibodies): To detect a circulating malignant clone and to assess immunocompetence by quantifying the level of CD8-expressing lymphocytes
- Human immunodeficiency virus (HIV) and human T-lymphotropic virus type 1 (HTLV-I) testing

For a diagnosis of Sézary syndrome, one or more of the following criteria should be met:

- Absolute Sézary cell count of at least 1 000 cells/µL
- Immunophenotypic abnormalities (expanded CD4+ T-cell population resulting in CD4/CD8 ratio of >10; loss of any or all of T-cell antigens CD2, CD3, CD4, and CD5; or loss of both CD4 and CD5)
- T-cell clone in the peripheral blood shown by molecular or cytogenetic methods: Flow cytometry may be useful for differential diagnosis of precursor and peripheral T-cell and NK-cell lymphomas

Imaging studies

- Chest radiography: To determine whether there is lung involvement
- Abdominal/pelvic computed tomography (CT) scanning: In patients with advanced mycosis fungoides (stage IIB to IVB) or those with clinically suspected visceral disease
- Positron emission tomography (PET) scanning: To determine visceral involvement

(Medscape).

Staging of Mycosis Fungoides (MF)

Staging describes the severity of a person's cancer based on the size and/or extent (reach) of the original (primary) tumour and whether or not cancer has spread in the body. Staging is important for several reasons:

- Staging helps the doctor plan the appropriate treatment.
- Cancer stage can be used in estimating a person's prognosis.
- Knowing the stage of cancer is important in identifying clinical trials that may be a suitable treatment option for a patient.
- Staging helps health care providers and researchers exchange information about patients; it also gives them a common terminology for evaluating the results of clinical trials and comparing the results of different trials.

Staging is based on knowledge of the way cancer progresses. Cancer cells grow and divide without control or order, and they do not die when they should. As a result, they often form a mass of tissue called a tumour. As a tumour grows, it can invade nearby tissues and organs. Cancer cells can also break away from a tumour and enter the bloodstream or the lymphatic system. By moving through the bloodstream or lymphatic system, cancer cells can spread from the primary site to lymph nodes or to other organs, where they may form new tumours. The spread of cancer is called metastasis.

All cancers are staged when they are first diagnosed. This stage classification, which is typically assigned before treatment, is called the clinical stage. A cancer may be further staged after surgery or biopsy, when the extent of the cancer is better known. This stage designation (called the pathologic stage) combines the results of the clinical staging with the surgical results.

A cancer is always referred to by the stage it was given at diagnosis, even if it gets worse or spreads. New information about how a cancer changes over time simply gets added on to the original stage designation. The cancer stage designation does not change (even though the cancer itself might) because survival statistics and information on treatment by stage for specific cancer types are based on the original cancer stage at diagnosis.
(National Cancer Institute).

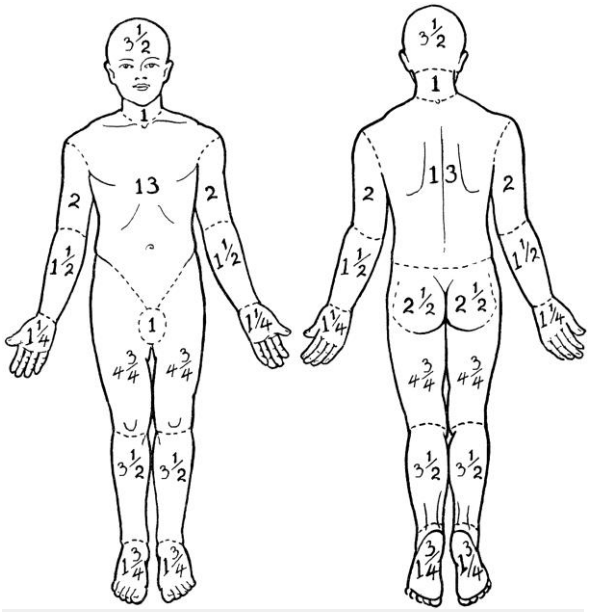
TNMB Stages

Skin T1	Limited patches*, papules and/or plagues† covering <10% of the skin surface. May further stratify into T1a (patch only) vs T1b (plaque ± patch)
T2	Patches, papules or plaques covering ≥ 10% of the skin surface. May further stratify into T2a (patch ony) vs Tsb (plaque ± patch)
T3	One or more tumours‡ (≥ 1cm diameter)
T4	Confluence of erythema covering ≥ 80% body surface area
Node N0	No clinically abnormal peripheral lymph nodes §; biopsy not required
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N1a	Clone negative #
N1b	Clone positive #
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3
N2a	Clone negative #
N2b	Clone positive #
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN_4; clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation ¶ and organ involved should be specified
Blood B0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical(Sézary) cells ‖
B1	Low blood tumour burder: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2
B1a	Clone negative #
B1b	Clone positive #
B2	High blood tumour burden: ≥ 1000/µL Sézary cells ‖ with positive clone #

* For skin, patch indicates any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloederma should be noted.
† For skin, plaque indicates any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloederma should be noted. Histologic features such as folliculotropism or large-cell transformation (> 25% large cells), $CD30^+$ or $CD30^-$, and clinical features such as ulceration are important to document.
‡ For skin, tumour indicates at least one 1-cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large-cell transformation has occurred. Phenotyping for CD30 is encouraged.

§ For node, abnormal peripheral lymph node(s) indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or 1.5 cm or larger in diameter. Node groups examined on physical examination include cervical, supraclavicular, epitrochlear, axillary, and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N_3 histopathologically.
¶ For viscera, spleen and liver may be diagnosed by imaging criteria.
‖ For blood, Sézary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sézary cells are not able to be used to determine tumour burden for B_2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: (1) expanded $CD4^+$ or $CD3^+$ cells with CD4/CD8 ratio of 10 or more, (2) expanded $CD4^+$ cells with abnormal immunophenotype including loss of CD7 or CD26.
A T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene.
(American Society of Hematology).

Calculating Body Surface Area



Regional percent body surface area (BSA) in the adult.
(Blood Journal).

Treatment of Mycosis Fungoides (MF)

Although one may be managed by a general dermatologist, MF is such a rare disease that treatment by a team of specialists is more appropriate.

The treatment team ideally should consist of physicians from different medical specialties:

- dermatologist who specialises in lymphoma
- medical oncologist
- radiation oncologist
- dermatopathologist

The simplest way to think about the multiple treatments available for MF is by dividing them into two categories: skin-directed therapies versus systemic therapies.

Skin-directed therapies are aimed at the skin primarily. The major treatments in this category include topical chemotherapy agents (nitrogen mustard or Mustargen), topical

corticosteroids, topical retinoids (Targretin gel), phototherapy (PUVA, UVB), and electron beam radiation.

Systemic therapies are administered by mouth or injection and are aimed at treating the skin and/or internal organs affected or at risk. These include chemotherapy agents and biologic response modifiers (oral retinoids, interferons, fusion proteins, or extracorporal photopheresis).

Commonly, multiple treatments may be used together, which is called Combined Modality Therapy (CMT).

For each treatment option, the following paragraphs include information on treatment indications, practical use of the therapy, and potential side effects.

Topical chemotherapy - the most commonly used topical chemotherapy agent is mechlorethamine (Mustargen or nitrogen mustard). This treatment involves applying the medication to the skin once or twice a day and is commonly applied to the entire body or body regions. This topical ointment needs to be prepared by a pharmacist, which specially compounds the medication. Room temperature or refrigerated storage is recommended.

Topical chemotherapy is a common first line therapy in patch or plaque lesions.

Side effects of Mustargen may include an allergic contact dermatitis, irritation, and itchiness.

Topical Retinoids - another skin directed therapy is topical retinoids. Bexarotene (Targretin) gel is a topical medication, which was approved by the Federal Drug Administration (FDA) for use in MF. Bexarotene is a derivative of Vitamin A. It works by changing the growth and maturation pattern of MF cells. Targretin gel is applied only to areas of skin affected by MF once or twice a day.

Targretin gel is most commonly indicated in limited patch or plaque disease. It can also be used in combination with other therapies for lesions, which may be more resistant to therapy. Side effects include local irritation or itchiness. Extreme redness can be seen, but it is commonly not painful or irritated. This is called retinoid erythema and is a normal manifestation of the treatment that may be seen. Sometimes, discontinuation of the gel is required, so the skin can be evaluated for any residual disease without the redness from the medication confusing the skin appearance. There is no systemic absorption, so the use of contraception in child-bearing women is not required, as it is for the pill form of Targretin. If one was to become pregnant while using Targretin gel, it is recommended to contacting one's physician immediately.

Topical Corticosteroids - topical corticosteroids can be used to treat mild, patch stage MF. The mechanism of action is not exactly known, but studies suggest the growth and maturation pattern of MF cells is modified. Topical corticosteroids vary in strength, with Class I (e.g., Ultravate or Lidex ointment) being the strongest to Class VI being the weakest (e.g., Desowen ointment). They come in lotions, creams, or ointments. Choosing the strength of the topical sometimes depends on where it will be applied on the body. In general, a weaker steroid would be used in more sensitive areas, such as the face, axilla, or groin region. They can be applied once or twice a day.

Topical corticosteroids can be used to treat individual skin lesions. Application to the entire skin, as with Mustargen ointment, is not indicated for corticosteroids.

Side effects include thinning of the skin, superficial blood vessels, easy bruising, and possible systemic absorption if used chronically. Long-term use of topical corticosteroids in MF is not recommended secondary to the potential side effects from continual use.

PUVA - PUVA is a therapy where a natural occurring plant product called psoralen (oxpsoralen) is used in combination with ultraviolet light therapy, specifically the long wavelength form called UVA. Oxpsoralens makes the T-cells of MF more sensitive to ultraviolet light, which enhances the effect of UVA on clearing the skin.

Typically, one will take the oxpsoralen by mouth (which is dosed by body weight) one and a half hours before receiving the light therapy. It is necessary that the patient protects his/her eyes and exposed skin areas with UV-wrap around glasses, protective clothing, or sunscreen between ingesting the oxpsoralens and the next 24 hours. The UVA light therapy is delivered in specialised light boxes. The UVA dosage is adjusted according to skin type, and the length of time in the box ranges from seconds to minutes. Patients will be required to have an eye examination prior to starting the therapy because of the increased risk of cataracts with long-term exposure to PUVA therapy. A common initial treatment schedule for PUVA is three times a week (three visits to the clinic each week to receive the light therapy). The frequency of therapy can be decreased as the skin improves.

PUVA is used commonly as first line treatment in patch or plaque skin lesions. It is also used commonly in combination with other treatments for more extensive disease. Possible side effects include nausea and increased risk of cataracts from the psoralen. UVA causes redness of the skin, itchiness, or dry skin. There is an increased risk for developing non-melanoma skin cancers and a possible increased risk of developing melanoma from exposure to PUVA.

Electron Beam Radiation and Local Radiation - mycosis fungoides is very sensitive to radiation. Electron beam radiation is a form of radiation where the beam does not penetrate deeper than the skin. This is a therapy, which treats the total skin. Patients are placed in multiple positions 2 to 3 metres from the radiation machine - linear accelerator, so all the skin is exposed. Typical treatment schedules last about 10 weeks, 4 times a week. Importantly, this treatment requires a special centre with the proper equipment and technique.

Electron beam radiation is a very effective first line treatment for treating patches, plaques, or tumours. Radiation treatment can also be delivered locally to treat specific skin lesions, which have been resistant to other therapies.

Side effects include redness, swelling, temporary nail loss, temporary hair loss, abnormal sweating, chronic dryness, and an increased risk of developing non-melanoma skin cancers.

Oral retinoids - retinoids are a class of drugs that are derivatives of vitamin A. These medications are effective in MF because they can change the growth and maturation pattern of MF cells.

Bexarotene (Targretin) is the most commonly used oral retinoid for MF. Each capsule is 75 mg. The capsules are usually taken all together, preferably after dinner. Retinoids are used to treat widespread patch, plaque, or tumorous skin lesions. They are also used in combination with other treatment modalities.

Because this is a systemic medication with several potential side effects, close monitoring is required while on the medication. This includes blood tests to monitor liver function, lipid levels, thyroid function, and blood counts. Bexarotene (Targretin) in particular can affect one's lipids significantly, and a medication to control triglyceride levels will be required. It can also cause decreased production of thyroid hormone, so commonly, patients are started on supplemental thyroid hormone. *Use of these medications for women of childbearing age is contraindicated*. Contraception is essential before, during, and for a period of time after the use of oral retinoids.

Other side effects of bexarotene (Targretin) include headache, loss of strength, nausea, rash, itch, skin flushing, dry skin, and dry mouth.

Interferon alpha - interferon alpha has been shown to be effective in treating patients with MF. It works by altering the immune system response. Interferon alpha is an injection which is given just under the skin, similar to insulin injections. It is typically delivered three times a week with gradual increases in the dose to therapeutic levels.

Interferon is used to treat widespread patch, plaque, or tumorous skin lesions. It is also commonly used in combination with other therapies.

Side effects include flu-like symptoms, fatigue, depression, weight loss. Periodic monitoring of the blood may be required to follow blood counts and thyroid function.

Fusion proteins - in 1999, the FDA approved a recombinant fusion protein called denileukin diftitox (Ontak) as a therapy for MF. It works by killing lymphocytes that have a certain immune receptor. The T-cells of MF often have this receptor. This medication is delivered intravenously typically over a 3 hour period in an outpatient setting. The schedule for this medication is that it is usually given 5 consecutive days every 3 weeks.

Ontak is not typically used as a first line therapy. It is reserved for refractory cases of widespread patch, plaque, or tumorous skin lesions.

Side effects include flu-like symptoms or acute infusion related events, such as transient low blood pressure, muscle aches, or vascular leak syndrome.

Extracorporal photopheresis - extracorporal photopheresis (ECP) is a way of delivering PUVA-like therapy to the skin, blood, and lymph nodes. As noted previously, PUVA therapy employs an oral medication called psoralen, which works by making the T-cells of MF more sensitive to ultraviolet light, in combination with UVA, ECP utilises the same principles of treatment, but the UVA portion in ECP is directed at white blood cells, which are collected temporarily outside the body, instead of the skin (as with PUVA therapy).

The blood is extracted intravenously and mixed with a liquid form of psoralens, exposed to UVA light, and returned to the body intravenously again. It is extracted in increments and the whole process takes a few hours each day in a special nursing area. It is usually transfused

over a two day period. The patient is usually not required to stay overnight in the hospital. The frequency of treatments is initially every 2-4 weeks, then less frequently as the skin improves.

ECP is a first line therapy for treating erythroderma . It is not as effective in treating patches, plaques, or tumours.

Side effects are minimal. These include temporary low-grade fever and slight malaise.

Systemic chemotherapy agents - systemic chemotherapy agents are usually reserved for MF that have failed skin-directed or systemic biologic therapies or have disease that extended to lymph nodes or other internal organs. Common agents include cyclophosphamide, adriamycin or Doxil, gemcitabine, methotrexate, and pentostatin.

Chemotherapy may be given as a single agent or multi-agent regimen. A detailed discussion of each agent is beyond the scope of this Fact Sheet. The side effects can be significant. Close monitoring of laboratory studies and general medical condition is necessary.
(Stanford School of Medicine).

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 condition or situation. Readers of this document should seek appropriate medical advice prior to taking or refraining from taking any action resulting from the contents of this Fact Sheet. As far as permissible by South African law, the Cancer Association of South Africa (CASNA) accepts no responsibility or liability to any person (or his/her dependants/estate/heirs) as a result of using any information contained in this Fact Sheet.

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