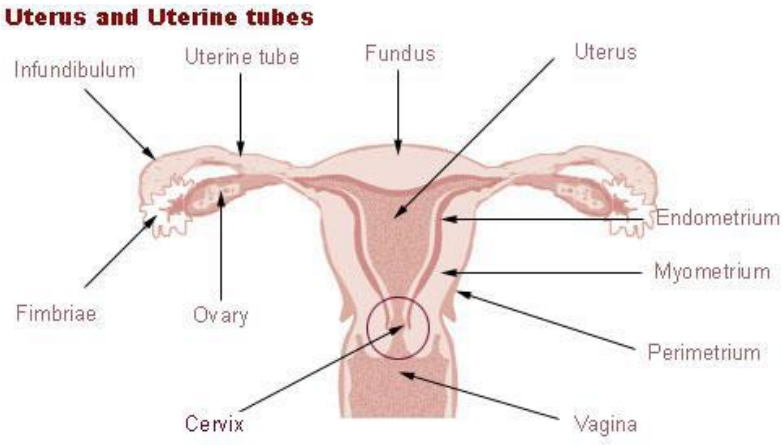
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet and Position Statement on Cervical Cancer

Introduction

The cervix is the lower, narrow end of the uterus (the hollow, pear-shaped organ where a foetus can grow). The cervix leads from the uterus to the vagina (birth canal) below. The cervix is sometimes referred to as the *uterine cervix*. The part of the cervix closest to the body of the uterus is called the *endocervix*. The part next to the vagina is the *exocervix*.



[Picture credit: Female Reproductive System]

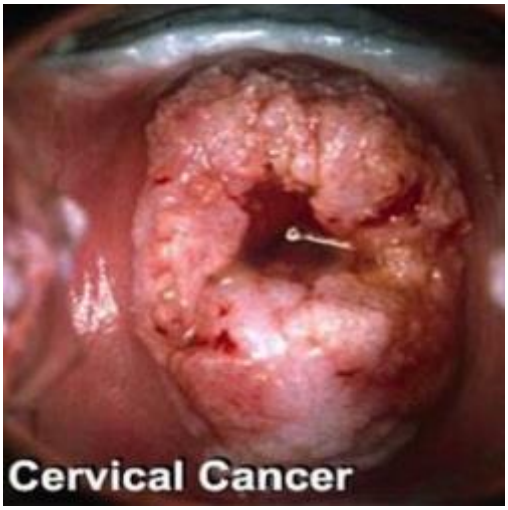
Worldwide, cervical cancer is the third most common type of cancer in women. It is much less common in developed countries like the United States of America because of the routine use of Pap smears by most women (PubMed).

Cervical cancer tends to appear during midlife. Over half of the women diagnosed are between the ages of 35 and 55. It rarely occurs in women under 20 and only 20% of the infected women are over 65 years of age (CervicalCancer.org).

Cervical Cancer

Cervical cancer is a malignant neoplasm arising from cells originating in the cervix. One of the most common symptoms of cervical cancer is abnormal vaginal bleeding, but in some cases there may be no obvious symptoms until the cancer has progressed to an advanced stage. Cervical cancer is a disease in which cells in the cervix become malignant (cancerous). The two main types of cells covering the cervix are *squamous cells* (on the *exocervix*) and *glandular cells* (on the *endocervix*). The place where these two cell types meet is called the *transformation zone*. Most cancers start in the transformation zone of the cervix (American Cancer Society; National Cancer Institute).

[Picture Credit: Cervical Cancer]



Cervical cancer is cancer that forms in tissues of the cervix. It is usually a slow-growing cancer that may not have immediate symptoms but can be found with regular Pap smear tests (a procedure in which cells are scraped from the cervix and looked at under a microscope). Cervical cancer is almost always caused by Human Papillomavirus (HPV) infection (National Cancer Institute; PubMed).

Cervical cancer starts as a pre-cancerous condition called dysplasia. This pre-cancerous condition can be detected by a Pap smear and is 100% treatable. That is why it is so important for women to get regular Pap smears done. Most women who are diagnosed with cervical cancer today have not had regular Pap smears or they have not followed up on abnormal Pap smear results.

Undetected pre-cancerous changes can develop into cervical cancer. From there is can spread to the bladder, intestines, lungs, and liver. It can take several years for pre-cancerous changes to turn into cervical cancer. Patients usually start experiencing problems when the cancer is already advanced and has spread (PubMed).

Incidence of Cervical Cancer in South Africa

According to the National Cancer Registry (2012) the following number of cervical cancer 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	5 785	1:39	15,37%
Asian females	72	1:90	6,67%
Black females	4 891	1:32	29,62%
Coloured females	350	1:61	8,39%
White females	472	1:70	2,97%

The frequency of histologically diagnosed cases of cervical cancer 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	85	811	1 470	1 426	947	581	157
Asian females	0	0	10	14	17	9	15	2
Black females	1	68	675	1 232	1 163	805	501	226
Coloured females	0	4	48	85	108	65	21	12
White females	0	13	74	128	126	67	40	17

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 of Cervical Cancer
Almost all cervical cancers are caused by HPV. HPV is a common virus that is spread through skin-to-skin contact, body fluids and sexual intercourse. There are many different types of HPV. Some strains lead to cervical cancer. Other strains may cause genital warts, while others do not cause any problems at all (PubMed).

Genital Human Papillomavirus (HPV) is the most common sexually transmitted infection in the world. More than 100 HPV types have been identified, over 40 of which can infect the genital area. HPV types are classified by their association with cancer:

Non-oncogenic (low-risk HPV) – such as HPV 6 and HPV 11
It can cause:

- Benign or low-grade abnormalities of cervical cells
- Anogenital warts
- Recurrent Respiratory Papillomatosis – a disease of the respiratory tract

Ongonenic (high-risk HPV) – such as HPV 16 and HPV 18
It can cause:

- Intraepithelial neoplasia of the anogenital region
- Cervical cancer
- Vulva cancer
- Vaginal cancer
- Penile cancer
- Anal cancer
- Oropharyngeal cancers

(Centres for Disease of Control and Prevention)

Cervical cancer is the second most common cancer in women worldwide, with about 500 000 new cases and 250 000 deaths each year, according to the World Health Organization (WHO). Virtually all cases are linked to genital infection with HPV, the most common viral infection of the reproductive tract.

High and Low Risk Human Papilloma Viruses
Most people infected with HPV never develop any symptoms, however, there are a number of conditions that can result from an HPV infection.

HPV Research Scientists have separated HPV types into those that are more likely to develop into cancer and those that are less likely. The so-called ‘high-risk’ types are more likely to lead to the development of cancer, while ‘low-risk’ viruses rarely develop into cancer.

The sexually transmitted varieties of ‘high-risk’ HPV types include:

HPV-16	HPV-18	HPV-31	HPV-33	HPV-35	HPV-39
HPV-45	HPV-51	HPV-52	HPV-56	HPV-58	HPV-59
HPV-68	HPV-69				

A few other HPV types are also sometimes included on this list. These ‘high-risk’ HPV types cause growths that are usually flat and nearly invisible as compared to the warts caused by types HPV-6 and HPV-11. Up to 70% of cervical cancer cases are caused by HPV-16 and HPV-18.

'Low-risk' HPV types can cause no symptoms or may cause conditions such as genital warts, but do not cause cervical cancer. Warts can form weeks, months, or even years after sexual contact with a person who has genital HPV. It is also possible that warts may never appear. In fact, most people with 'low-risk' HIV types never know they are infected because they do not get warts or any other symptoms.

The following table lists various conditions along with their associated types of HPV:

Disease	**HPV Type**
Cervical cancer	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58
Precancerous changes	16, 18, 34, 39, 42, 55
Laryngeal papillomas	6, 11, 30
Genital Warts	6, 11, 30, 40, 41, 42, 43, 44, 45, 51, 54
Common warts	1, 2, 4, 26, 27, 29, 41, 57
Flat warts	3, 10, 27, 28, 41, 49
Plantar warts	1, 2, 4

(eMedTV).

CANSA's Position:

CANSA:

- is in favour of vaccinating all prepubescent girls against HPV
- commends and requests the South African Government, National Department of Health, and National Department of Basic Education to continue the HPV vaccination programme started in 2014 whereby every girl in Grade 4 (9 years) to be vaccinated against HPV at no cost

Signs and Symptoms of Common Gynaecologic Problems

Early on, cervical cancer may not cause signs and symptoms. Advanced cervical cancer may cause bleeding or discharge from the vagina that is not normal, such as bleeding after sex. If any of these signs are present, a medical doctor should be consulted. The cause may be something other than cancer, but the only way to know is to consult a medical doctor.

Gynaecologic Cancer Symptoms

Symptom	Cervical Cancer	Ovarian Cancer	Uterine Cancer	Vaginal Cancer	Vulva Cancer
Abnormal vaginal bleeding or discharge	▪	▪	▪	▪	
Pelvic pain or pressure		▪	▪		
Abdominal or back pain		▪			
Bloating		▪			
Having to pass urine often		▪		▪	
Itching or burning of the vulva					▪
Changes in vulva colour or skin such as a rash, sores or warts					▪

(Centers for Disease Control and Prevention)

Risk Factors for Cervical Cancer
Even though HPV infection is the major cause of cervical cancer, several risk factors are linked to the development of cervical cancer.

Risk factors for cervical cancer include:

- Having sex at an early age
- Having many sexual partners
- Having first sexual intercourse at a young age
- Smoking tobacco products increases one's risk
- Using oral contraceptives
- Having a weakened immune system
- Poor economic status (may not be able to afford regular Pap smears or have limited access to screening services)
- Sexual partners who have multiple partners or who participate in high-risk sexual activity
- parity – HPV is less common among women with decreased parity
- women who smoke are more susceptible to cervical cancer than women who do not smoke
- failure to always use barrier methods during sexual intercourse, and
- ineffective management and treatment of sexually transmitted infections (STI's)
- Women whose mothers took the drug DES (diethylstilbestrol) during pregnancy in the early 1960's to prevent miscarriage

(National Cancer Institute; PubMed).

<u>CANSA supports:</u>

- all efforts to assist women to quit smoking or preferably never to start smoking
- promotion of the use of barrier methods during intercourse to prevent the spread of HPV and other sexually transmitted infections (STI's) including HIV
- the promotion of the postponement of sexual activity to older age
- the effective management and treatment of sexually transmitted infections (STI's) and
- decreasing parity.

Types of Cervical Cancer
There are two main types of cervical cancer: squamous cell carcinoma and adenocarcinoma. Each one is distinguished by the appearance of cells under a microscope.

- Squamous cell carcinomas begin in the thin, flat cells that line the bottom of the cervix. This type of cervical cancer accounts for 80 to 90 percent of cervical cancers.

- Adenocarcinomas develop in the glandular cells that line the upper portion of the cervix. These cancers make up 10 to 20 percent of cervical cancers.

Sometimes, both types of cells are involved in cervical cancer. Other types of cancer can develop in the cervix, but these are rare.

- Metastatic cervical cancer is cancer that has spread to other parts of the body.

(Cancer Treatment Centers of America).

Referral Criteria
For any primary health care service to operate effectively a referral system needs to be in place.

The referral system must make provision for:

- Clients with a normal Pap smear to be informed of their next Pap smear date
- Any client with a microscopically suspicious lesion, whatever the cytological result, should be referred for colposcopy

CANSA's Position:
CANSA supports the above referral criteria.

CANSA has an organised cervical screening programme that services many women in rural and previously disadvantaged areas in South Africa. This service is offered using mobile health clinics manned by professional nurses. They work in close collaboration with the National Department of Health (NDoH), National Health Laboratory Services (NHLS) and private laboratories on agreement.

Staging of Cervical Cancer
A very important factor in determining the prognosis 9outcome) of cervical cancer is how early the cancer is detected to determine how far it has spread. Regular pelvic examinations and Pap smear screening improves the chances of detecting any abnormality or pre-cancerous lesions. A patient's chances of survival decreases if the cervical cancer is not detected early enough and commenced spreading to other parts of the body.

The various stages of cervical cancer also affect the chance of recovery or prognosis of the patient.

Staging is a way of describing where the cancer is located, if or where it has spread, and whether it is affecting the functions of other organs in the body. Doctors use diagnostic tests to determine the cancer's stage, so staging may not be complete until all of the tests are finished. Knowing the stage helps the doctor to decide what kind of treatment is best and can help predict a patient's prognosis (chance of recovery). There are different stage descriptions for different types of cancer.

One tool that doctors use to describe the stage is the TNM system. This system judges three factors: the tumour itself, the lymph nodes around the tumour, and if the tumour has spread to the rest of the body. The results are combined to determine the stage of cancer for each person. There are five stages: stage 0 (zero) and stages I through IV (one through four). The stage provides a common way of describing the cancer, so doctors can work together to plan the best treatments.

TNM is an abbreviation for tumour (T), node (N), and metastasis (M). Doctors look at these three factors to determine the stage of cancer:

- How large is the primary tumour and where is it located? **(Tumour, T)**
- Has the tumour spread to the lymph nodes? **(Node, N)**
- Has the cancer metastasised to other parts of the body? **(Metastasis, M)**

Tumour. Using the TNM system, the "T" plus a letter or number (0 to 4) is used to describe the size and location of the tumour. Some stages are divided into smaller groups that help describe the tumour in even more detail. The Roman numerals in parentheses are stages used in another widely used staging system from the *Federation Internationale de Gynecologie et d'Obstetrique*, or FIGO.

TX: The primary tumour cannot be evaluated. More tests may be needed.
T0: There is no primary tumour.
Tis: This stage is called carcinoma (cancer) in situ, which means that the cancer is found only in the layer of cells lining the cervix and has not spread deeper into the cervix.
T1/FIGO I: The carcinoma is found only in the cervix.
T1a/FIGO IA: Invasive carcinoma was diagnosed only by microscopy (viewing cervical tissue or cells under a microscope).

Note: Any tumour found macroscopically (large enough to be recognized by imaging tests or to be seen or felt by the doctor) is called stage T1b or FIGO IB.
T1a1/FIGO IA1: There is a cancerous area of 3.0 millimetres (mm) or smaller in depth, and 7.0 mm or smaller in length.
T1a2/FIGO IA2: There is a cancerous area larger than 3.0 mm but not larger than 5.0 mm in depth, and 7.0 mm or smaller in length.
T1b/FIGO IB: In this stage, the doctor can see the lesion, and the cancer is found only in the cervix, **or** there is a microscopic lesion (one able to be seen using a microscope) that is larger than a stage T1a2/FIGO IA2 tumour (see above). The cancer may have been found because of a physical examination, laparoscopy, or other imaging methods (see Diagnosis).
T1b1/FIGO IB1: The tumour is 4.0 centimetres (cm) or smaller.
T1b2/FIGO IB2: The tumour is larger than 4.0 cm.
T2/FIGO II: The cancer has grown beyond the uterus but not to the pelvic wall or to the lower third of the vagina.
T2a/FIGO IIA: The tumour has not spread to the tissue next to the cervix, also called the parametrial area.
T2a1/FIGO IIA1: The tumour is 4.0 cm or smaller.
T2a2/FIGO IIA2: The tumour is larger than 4.0 cm.
T2b/FIGO IIB: The tumour has spread to the parametrial (tissue surrounding the uterus) area.
T3/FIGO III: The tumour extends to the pelvic wall, and/or involves the lower third of the vagina, and/or causes hydronephrosis (swelling of the kidney) or a non-functioning kidney.
T3a/FIGO IIIA: The tumour involves the lower third of the vagina, but it has not grown into the pelvic wall.
T3b/FIGO IIIB: The tumour has grown into the pelvic wall and/or causes hydronephrosis or non-functioning kidneys.
T4/FIGO IVA: The tumour has spread to the mucosa (lining) of the bladder or rectum and grown beyond the pelvis.

Node. The 'N' in the TNM staging system stands for lymph nodes, the tiny, bean-shaped organs that help fight infection. Lymph nodes near the cervix are called regional lymph nodes. Lymph nodes in other parts of the body are called distant lymph nodes.
NX: The regional lymph nodes cannot be evaluated.
N0 (N plus zero): The tumour has not spread to the regional lymph nodes.

N1/FIGO IIIB: The tumour has spread to the regional lymph node(s).

Distant metastasis. The 'M' in the TNM system indicates whether the cancer has spread to other parts of the body.

M0 (M plus zero): There is no distant metastasis.
M1/FIGO IVB: There is distant metastasis.

The four (4) numeric stages of cervical cancer are as follows:

Stage I The cancer is confined to the cervix area
Stage II The cancer has spread beyond the cervix but is confined to the pelvic area
Stage III The cancer has spread to the pelvic wall or lower part of the vagina
Stage IV The cancer has spread to other organs or parts of the body

Some clinicians use a system of staging where various sub-groups are introduced to differentiate staging further.
(CervicalCancer.Org; CancerHelp UK; Cancer.Net).

Cervical Cancer Survival Rates

There are many different factors that affect the prognosis (outlook) of cervical cancer including the stage of the cancer, the age of the patient, and general health of the patient. Use is mostly made of the 5-year survival rate. This rate refers to the percent of patients who live at least 5 years after their cancer is found. Many of these patients live much longer than 5 years (American Cancer Society).

The following 5-year survival rate is based on figures obtained from the United States of America (CervicalCancer.Org). They can, however, provide some valuable information for individuals who have a particular interest in wanting to know what the possible 5-year survival rate is.

Stage IA 95% of affected women will be alive 5 years after diagnosis
Stage IB 85 to 90% of affected women will be alive 5 years after diagnosis
Stage IIA 75 to 80% of affected women will be alive 5 years after diagnosis
Stage IIB 75% of affected women will be alive 5 years after diagnosis
Stage III 50% of affected women will be alive 5 years after diagnosis
Stage IVA 20% of affected women will be alive 5 years after diagnosis
Stage IVB less than 10% of affected women will be alive 5 years after diagnosis

Overall about 7 out of 10 women (70%) will remain alive 5 years after diagnosis. Younger women have a higher survival rate than older women. Some studies indicate that adding chemotherapy to treatment plans increases survival rates by 50% for locally invasive cervical cancer.

Many developing nations have an overall survival rate of less than 40% (CervicalCancer.Org).

Signs and Symptoms of Cervical Cancer

Approximately 75% of patients are diagnosed with *squamous cell* cervical cancer and approximately 10% have *adenocarcinoma* cervical cancer. A much smaller number of patients develop a form of cancer containing elements of both types (CervicalCancer.Org).

Early signs and symptoms of cervical cancer

In women who receive regular Pap screening, the first finding of the disease is usually an abnormal Pap test result (CervicalCancer.Org).

Early symptoms that may occur can include

- Abnormal vaginal bleeding between periods, after intercourse, or after menopause
- Any bleeding after menopause
- Continuous vaginal discharge, which may be pale, watery, pink, brown, bloody or foul-smelling
- Periods becoming heavier and lasting longer than usual

(PubMed)

Signs and symptoms of progressed cervical cancer
Some of the common symptoms observed during the later stages of cervical cancer are:

- Vaginal bleeding after sexual intercourse
- Pelvic pain
- Pain during sexual intercourse
- Offensive vaginal discharge may occur (pink, pale, brown, blood streaked, and foul-smelling)
- Abnormal bleeding between menstrual periods
- Heavy bleeding during menstrual period
- Increased urinary frequency
- Bleeding after menopause
- Painful urination
- Pelvic pain that is not related to the normal menstrual cycle
- Low back pain
- Leg pain
- Single swollen leg
- Bone fractures
- Weight loss
- Urethritis or urinary infection can be a sign of cervical cancer

(Mayo Clinic: CervicalCancer.Org; About.com; PubMed).

Diagnosis of Cervical Cancer
The following procedures may be used:

<u>*Pap smear*</u> – This is a procedure whereby cells from the surface of the cervix are collected. The cells are viewed under a microscope, after staining, to find out if the cells are abnormal. This procedure is also called a Pap test. It is short for Papanicolaou (1947) with reference to George Nicholas Papanicolaou (1883-1962), a Greek-born United States anatomist who developed the technique of staining and examining collected cells to test for cervical cancer (Dictionary.Com).

<u>*Human Papillomavirus (HPV) Test*</u> – A laboratory test used to check DNA for certain types of HPV infection. Cells are collected from the cervix and checked to find out if an infection is caused by a type of HPV that is linked to cervical cancer. It is also called the HPV DNA Test.

The cobas® HPV Test - is the only clinically validated, FDA-approved assay that simultaneously provides pooled results on high-risk genotypes and individual results on the highest-risk genotypes, HPV 16 and HPV 18. This test is a qualitative *in vitro* test for the detection of Human Papillomavirus (HPV) in patient specimens. The test utilises amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridisation for the detection of 14 high-risk (HR) HPV types in a single analysis.

The test specifically identifies (types) HPV 16 and HPV 18 while concurrently detecting the rest of the high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) at clinically relevant infection levels. Specimens are limited to cervical cells collected in cobas® PCR Cell Collection Media (Roche Molecular Systems, Inc.), PreservCyt® Solution (Cytyc Corp.) and SurePath® Preservative Fluid (not approved in the US) (BD Diagnostics-TriPath).

Characteristics of the cobas HPV test include:

- Simultaneously detects 14 high-risk HPV types and provides specific genotyping information for HPV Type 16 and 18
- A qualitative multiplex assay that provides specific genotyping information for HPV Types 16 and 18, while concurrently detecting the other 12 high-risk HPV types in a pooled result. ß-globin from cellular input is used as an internal control to assess specimen quality and identify specimens containing factors that inhibit the amplification process. This assay is automated on the cobas® 4800 System.

Features and Benefits of the cobas HPV test:

- Easy to learn, easy to use
- Reduces labour costs and training time
- Intuitive software walks the user through the entire set up process
- Bi-directional LIS connection protects results integrity and reduces repetitive tasks
- Automated result algorithm provides clear positive, negative or invalid results with no grey zone
- Quality control in every step
- A total process internal control utilising the ß-globin identifies samples with low cellularity that could lead to false negative results
- Contamination control
- The AmpErase enzyme degrades previously amplified target, allowing sample prep and detection in the same laboratory

Colposcopy – A procedure in which a colposcope (a lighted, magnifying instrument) is used to check the vagina and cervix for abnormal areas.

Biopsy – A sample of tissue is cut from the cervix and viewed under a microscope by a pathologist to check for signs of cancer, often referred to as *cone biopsy*.

Endocervical curettage (ECC) - to examine the opening of the cervix

Pelvic Examination – An examination of the vagina, cervix, uterus, fallopian tubes, ovaries, and rectum.
(National Cancer Institute)

Once a woman is diagnosed with cervical cancer, the medical practitioner will order more tests to determine how far the cancer has spread. This is part of staging and may include:

- Chest X-ray

- Computed Tomography (also called Computerised Axial Tomography or CT scan)
- Cystoscopy
- Intravenous Pyelogram (IVP)
- Magnetic Resonance Imaging (MRI)

(PubMed)

CANSA's Position Regarding Pap Smears

CANSA believes that it is ideal to have a Pap smear done 10-20 days after the start of the last period. It is not recommended to plan one's Pap smear during a period. Menstrual fluid and blood may make it difficult for the pathologist to interpret results. However, if the flow is light, some doctors will perform a Pap smear. Newer, liquid based Pap smears can separate cervical cells from mucus and blood, allowing a more accurate reading.

If a woman has started her period unexpectedly or finds that she has scheduled a Pap smear during a time when she may have her period, she should call her doctor's office. Ask to speak to a nurse or the doctor and inform them that the Pap smear will coincide with her period. It is best to reschedule an appointment.

It is also suggested that women avoid having anything in the vagina 24-48 hours prior to a Pap smear.
This includes:

- sexual intercourse
- spermicides, foams, or jellies
- douching
- vaginal inserts
- tampons

All of these things can make it difficult for the pathologist to accurately interpret results.

CANSA further believes that:

- every eligible woman should preferably have a Pap smear at least every 3 years
- it is better to have a Pap smear at a less-than-optimal time than not at all
- routine cervical screening is not required for women under 18 years of age, even if they are sexually active as there is no evidence to support encouraging women under 18 years of age to have a Pap smear
- all women who have ever been sexually active should start having Pap smears between the ages of 18 and 20 years, or one or two years after first having sexual intercourse, whichever is later
- a decision to screen a woman below the age of 18 years is at the discretion of the clinician and would depend on the individual circumstances of the patient
- Pap smears may cease at the age of 70 years for women who have had two normal Pap smears within the last five years
- Women over 70 years who have never had a Pap smear, or who request a Pap smear, should be screened

Treatment of Cervical Cancer
Treatment of cervical cancer depends on:

- The stage of the cancer
- The size and shape of the tumour
- The woman's age and general health
- Her desire to have children in the future

(PubMed)

Treatment of early-stage cervical cancer may include:

- Cervical Conisation – it involves removing a cone-shaped piece of tissue from the cervix and cervical canal. The overall size of the tissue removed will vary depending on the severity of the cancer
- Loop Electrosurgical Excision Procedure (LEEP) – use is made of a thin, low-voltage electrified wire loop to cut out abnormal tissue
- Cryosurgery – used for cervical dysplasia or abnormal cells on the cervix. If left untreated, these abnormal cells may develop into cervical cancer. Cryosurgery kills pre-cancerous and cancerous cells by freezing them
- Total hysterectomy (removal of the uterus)
- Internal Radiation Therapy (Brachytherapy)

(CervicalCancer.Org; University of Maryland Medical Center: CancerAbout.Com).

Treatment for more advanced cervical cancer may include:

- Radical hysterectomy – where the uterus and much of the surrounding tissues,, including lymph nodes and the upper part of the vagina is removed surgically
- Pelvic exenteration – an extreme type of surgery in which all of the organs of the pelvis, including the bladder and rectum, are removed surgically

(PubMed; University of Maryland Medical Center)

Radiation Therapy may be used to treat cancer that has spread beyond the pelvis, or cancer that has returned:

- Internal radiation therapy – where use is made of a device filled with radioactive material, which is placed inside the woman's vagina next to the cervical cancer – the device is removed before she is discharged to go back home
- External radiation therapy – where high-powered energy beams of radiation from a radiation device is focused onto the body where the cancer is located

(Mayo Clinic; PubMed; Cancer Treatment Centers of America)

Chemotherapy uses drugs to kill the cancer cells:
Chemotherapy drugs, which can be used alone or in combination with each other, are given to the patient. Sometimes radiation and chemotherapy are used before or after surgery (PubMed; Mayo Clinic).

Common chemotherapy medicines used to treat cervical cancer include:

- Cisplatin. Cisplatin is the medicine most often used in combination with radiation for cervical cancer.
- Fluorouracil (5-FU).

- Mitomycin.
- Paclitaxel.
- Ifosfamide.
- Carboplatin.
- Bevacizumab.
- Docetaxel.
- Epirubicin.

(WebMD)

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.
These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Locally Advanced Cervical Cancer[1a]

NOTE: All recommendations are category 2A unless otherwise indicated.

First-line Therapy[b]

REGIMEN	DOSING
Cisplatin[2,3]	Cisplatin 40mg/m^2 IV once weekly for up to 6 doses (total dose not to exceed 70mg per week).
Cisplatin + 5-FU[4,5]	**Days 1–5 of radiotherapy:** Cisplatin 75mg/m^2 IV over 4 hours, followed by 5-FU 4,000mg/m^2 IV over 96 hours (begin chemotherapy within 16 hours after radiotherapy). Repeat cycle every 3 weeks for 2 additional cycles. **OR** **Days 1 and 29:** Cisplatin 50mg/m^2 IV infusion (4 hours prior to external-beam radiotherapy) at 1mg/minute with standard hydration,**plus** **Days 2–5, and 30–33:** 5-FU 1,000mg/m^2 IV continuous infusion over 24 hours (total dose 4,000mg/m^2 each course).

Metastatic or Recurrent Cervical Cancer[1c]

First-line Combination Therapy[d]

Cisplatin + paclitaxel + bevacizumab (Category 1)[6]	**Day 1:** Cisplatin 50mg/m^2 IV + paclitaxel 135–175mg/m^2 IV + bevacizumab 15mg/kg IV. Repeat cycle every 21 days until disease progression, unacceptable toxicity, or complete response.
Paclitaxel + cisplatin (Category 1)[7,8]	**Day 1:** Paclitaxel 135mg/m^2 IV over 24 hours **Day 2:** Cisplatin 50mg/m^2 IV at a rate of 1mg/minute. Repeat cycle every 3 weeks for 6 cycles.
Topotecan + paclitaxel + bevacizumab (Category 1)[6]	**Day 1:** Paclitaxel 175mg/m^2 IV over 3 hours, followed by 1-hour carboplatin IV at AUC 5mg•mL/min. Repeat cycle every 3 weeks for a maximum of 6 cycles or until disease progression or unacceptable toxicity.
Paclitaxel + carboplatin (Category 1 for patients with prior cisplatin	**Day 1:** Paclitaxel 175mg/m^2 IV over 3 hours, followed by 1-hour carboplatin IV at AUC 5mg•mL/min.

therapy)[9,10]	Repeat cycle every 3 weeks for a maximum of 6 cycles or until disease progression or unacceptable toxicity.
Carboplatin + paclitaxel + bevacizumab[6,10]	**Day 1:** Paclitaxel 175mg/m^2 IV over 3 hours, followed by 1-hour carboplatin IV at AUC 5mg•mL/min + bevacizumab 15mg/kg IV. Repeat cycle every 3 weeks for a maximum of 6 cycles or until disease progression or unacceptable toxicity.
Cisplatin + topotecan[11]	**Days 1–3:** Topotecan 0.75mg/m^2 IV over 30 minutes, **followed by** **Day 1:** Cisplatin 50mg/m^2 IV. Repeat cycle every 3 weeks.
Topotecan + paclitaxel[6e]	**Days 1–3:** Topotecan 0.75mg/m^2 IV over 30 minutes, **followed by** **Day 1:** Paclitaxel 175 mg/m^2 IV.
Cisplatin + gemcitabine (Category 3)[12]	**Days 1 and 8:** Cisplatin 30mg/m^2 IV followed by gemcitabine 800mg/m^2 IV. Repeat cycle every 4 weeks.
Possible First-Line Single-Agent Therapy	
Cisplatin (preferred as a single agent)[8]	**Day 1:** Cisplatin 50mg/m^2 IV. Repeat every 3 weeks for 6 cycles.
Carboplatin[13]	**Day 1:** Carboplatin 400mg/m^2 IV. Repeat every 4 weeks.
Paclitaxel[14]	**Day 1:** Paclitaxel 250mg/m^2 IV over 3 hours. Repeat every 3 weeks.
Second-Line Therapy	
Note: Agents listed below are category 2B unless otherwise indicated.	
Bevacizumab[15]	**Day 1:** Bevacizumab 15mg/kg IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.
Albumin-bound paclitaxel (nab-paclitaxel)[16]	**Days 1, 8, and 15:** Nab-paclitaxel 125mg/m^2 IV over 30 minutes. Repeat cycle every 4 weeks until disease progression or unacceptable toxicity.
Docetaxel[17]	**Day 1:** Docetaxel 100mg/m^2 IV over 1 hour. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.
5-FU[18]	**Days 1–5:** Leucovorin 200mg/m^2 IV bolus + 5-FU 370mg/m^2 IV bolus every 4 weeks for the first 2 courses with subsequent courses given every 5 weeks.
Gemcitabine[19]	**Days 1, 8, and 15:** Gemcitabine 800mg/m^2 IV over 30 minutes, with a 1-week rest until disease progression or unacceptable toxicity.
Ifosfamide[20,21]	**Days 1–5:** Ifosfamide 1.5g/m^2 IV over 30 minutes; dose reduced to 1.2g/m^2 in patients with prior radiotherapy. Repeat cycle every 3 weeks.

Irinotecan[22]	Irinotecan 125mg/m^2 IV over 90 minutes weekly for 4 weeks. Repeat cycle every 6 weeks.
Mitomycin[23]	**Day 1:** Mitomycin 6mg/m^2 IV. Repeat cycle every 4 weeks.
Pemetrexed[24]	**Day 1:** Pemetrexed 900mg/m^2 IV over 10 minutes. Repeat cycle every 21 days.
Topotecan[25,26]	**Days 1–5:** Topotecan 1.5mg/m^2 IV. Repeat cycle every 3 to 4 weeks.
Vinorelbine[27]	**Days 1 and 8:** Vinorelbine 30mg/m^2; dose omitted on day 8 for grade 3 or 4 neutropenia **OR** reduced to 20 mg/m^2 for grade 2 neutropenia. Repeat cycle every 3 weeks.

[a] Includes patients with stage 2B to 4A disease, but can be extended to include patients with 1B2 and 2A2 disease in the advanced disease category.

[b] Given concurrently with pelvic radiotherapy and brachytherapy; category 1 for patients without nodal disease or with disease limited to the pelvis as determined through surgical staging. In patients with positive para-aortic and pelvic lymph nodes on imaging studies, extraperitoneal lymph node dissection should be considered, followed by extended-field radiotherapy, concurrent cisplatin-containing chemotherapy, and brachytherapy.

[c] Cisplatin, carboplatin, docetaxel, and paclitaxel may cause drug reactions, which can be managed following recommendations

in NCCN Guidelines for Ovarian Cancer—Management of Drug Reaction [OV-C].

[d] Cost and toxicity should be carefully considered when selecting an appropriate regimen for treatment.

[e] Although topotecan + paclitaxel was not shown to be superior to cisplatin + paclitaxel, it may be considered an alternative in patients who are not candidates for cisplatin.

(Cancer Therapy Advisor)

Immunotherapy in the Treatment of Cervical Cancer

Several approaches to T cell based-immunotherapy for cervical cancer have shown promise in early clinical trials.

As the fourth most frequently diagnosed cancer among women worldwide, cervical cancer is one of the major cancer types for which new immunotherapies are being developed and tested in clinical trials. Human papillomavirus virus (HPV) infection is one of the major causes of cervical cancer and is believed to cause almost all cases. This prevalent virus is also linked to other anal, genital, and head and neck cancers.

There is an imperative need for new and advanced immunotherapy treatments for cervical cancer. Though mortality rates have decreased due to effective use of Pap testing and DNA testing, people already infected with HPV or those who have already been diagnosed with cervical cancer do not benefit from the FDA-approved HPV vaccine Gardasil. Symptoms of this disease often go undetected until the cancer becomes invasive. For this reason, immunotherapy represents a unique opportunity for treating cervical cancer.

Thankfully, the targeted antibody bevacizumab has been approved for cervical cancer patients, and numerous other immunotherapy approaches have seen promising results in early-stage clinical trials, including T cell immune checkpoint inhibitors, therapeutic vaccines, and adoptive cell therapy/transfer.

Gardasil, got FDA approval in 2006, while a newer version of the vaccine, Gardasil-9®, was approved by the FDA in 2014. This revolutionary vaccine protects women against nine different types of HPV that ultimately lead to approximately 90% of all cases of cervical cancer across the globe.

Checkpoint Inhibitors/Immune Modulators - a promising avenue of clinical research in cervical cancer is the use of T cell immune checkpoint inhibitors. These treatments work by targeting molecules that serve as checks and balances in the regulation of T cell immune responses. By blocking inhibitory molecules or, alternatively, activating stimulatory molecules, these treatments are designed to unleash or enhance pre-existing anti-cancer T cell immune responses. Several checkpoint inhibitors, targeting multiple different checkpoints, are currently in development.

- Pembrolizumab (Keytruda®), a PD-1 antibody, is being tested in a phase II trial for patients with cervical, vulvar, or anal cancer.
- Nivolumab (Opdivo®), a PD-1 antibody, is being tested in a phase I/II for patients with viral-associated cancers, including cervical cancer, vaginal cancer, and vulvar cancer.
- Ipilimumab (Yervoy®), an anti-CTLA-4 antibody, is being tested in a phase I study of chemoradiation followed by ipilimumab for patients with locally advanced cervical cancer. One of the investigators on this trial—W. Martin Kast, Ph.D.—was awarded a CRI Clinic and Laboratory Integration Program (CLIP) grant to test if chemotherapy boosted ipilimumab in cervical cancer.
- Durvalumab (MEDI4736), an anti-PD-L1 antibody, is being tested in combination with tremelimumab, an anti-CTLA-4 antibody, in a phase I trial for patients with six kinds of cancer, including cervical cancer. This trial is sponsored jointly by the CRI/Ludwig Clinical Trials Network.

Therapeutic Vaccines - cancer vaccines are designed to elicit a T cell immune response against tumour-specific or tumour-associated antigens, encouraging the immune system to attack cancer cells bearing these antigens.

- A phase II clinical trial of TVGV-1 vaccine for patients with HPV-induced cervical pre-cancer.
- A phase I/II trial of VGX-3100, a vaccine that targets HPV types 16 and 18, and INO-9012, a DNA construct that induces human interleukin 12 (IL-12), are being tested in patients with cervical cancer.
- ADXS11-001, a vaccine against the E7 protein, which is made by HPV, is in phase I/II trials in patients with anal cancer.
- There are two phase I clinical trials testing pNGVL4a/E7 (Detox)/HSP70 DNA vaccine in patients with HPV16+ cervical intraepithelial neoplasia. The first one will determine the best dose and the second one will be a combination with imiquimod, an innate immune activator.

Adoptive Cell Therapy - another avenue of immunotherapy for cervical cancer is adoptive T cell transfer. In this approach, T cells are removed from a patient, genetically modified or treated with chemicals to enhance their activity, and then re-introduced into the patient with the goal of improving the T cell immune system's anti-cancer response. The following study is currently enrolling patients:

- A phase II study of white blood cells taken from the patient's own tumour for patients with HPV-related cancers, including cervical cancer.
- A phase II study of T cells genetically engineered to target HPV16 E6 in patients with cervical cancer, vaginal cancer, anal cancer, and penile cancer.
- A phase I study of T cells genetically engineered to be resistant to TGFβ, which the HPV-cancers produce, in patients with cervical cancer, vulvar cancer, anal cancer, and penile cancer.

Monoclonal Antibodies - monoclonal antibodies are molecules, generated in the lab, that target specific antigens on tumours. Bevacizumab (Avastin®), which targets vascular endothelial growth factor (VEGF) that helps tumours form new blood vessels to get nutrients (a process known as angiogenesis), is FDA approved for the treatment of recurrent or late-stage cervical cancer.

- HuMax®-TF-ADC, an antibody drug conjugate targeting tissue factor-specific cells, is being tested in two clinical trials in patients with advanced cancer, including cervical cancer.
- IMMU-132, an antibody drug conjugate targeting the TROP-2 antigen, which is expressed in a variety of cancers, is being tested in a phase I/II trial in patients with advanced cancer, including cervical cancer.

(Cancer Research Institute).

Follow-up Treatment

Follow-up checks will continue for some years after treatment. At first follow-up checks may be conducted every few months, becoming gradually less and less frequent.

Follow-up checks may include:

- Having a physical examination by the medical practitioner
- Pap smear
- Colposcopy
- Blood tests for tumour markers
- X-rays
- CT Scan or MRI scan

(CancerHelp UK)

Lowering the Risk for Cervical Cancer

Cancer prevention is action taken to lower the risk for getting cancer. The risk for cervical cancer can be lowered by:

- Having regular Pap smear tests – Current guidelines recommend that women should have a Pap test every 3 years beginning at age 21. These guidelines further recommend that women aged 30 to 65 should have HPV and Pap co-testing every 5 years or a Pap test alone every 3 years. Women with certain risk factors may need to have more frequent screening or to continue screening beyond age 65
- Having a Human Papilloma Virus (HPV) test - In women older than age 30, the Pap smear may be combined with a test for human papillomavirus (HPV) — a common sexually transmitted infection that can cause cervical cancer in some women
- Getting an HPV vaccine before becoming sexually active
- Not using tobacco products
- If smoking, to quit smoking
- Not having unprotected sexual intercourse
- Limiting the number of sexual partners
- Not becoming sexually active at a young age

(National Cancer Institute; Centers for Disease Control and Prevention; Mayo Clinic)

Cervical Cancer and HIV

There are approximately 5,7 million HIV+ people in South Africa of which 60% are women. They are at higher risk of HPV infection and persistence. Research shows that they are infected with a broader range of HPV strains. Research has also found that those who are treated with Highly Active Antiretroviral Therapy (HAART), have a longer lifespan and are at a significantly higher risk to develop cancer of the cervix.

CANSA's Position:

CANSA supports a non-discriminating approach and calls for the equal treatment of all individuals.

CANSA further supports:

- The education of health personnel concerning the importance of cervical screening;
- The training of health personnel in the correct taking of Pap smears;
- The training of professional nurses in cytology so that they can be used for the staining and screening of Pap smears;
- Ensuring that good records are kept concerning the quality and outcome of Pap smears, including a client recall system;
- Effective follow-up and referral of clients;
- Educating the community about the importance of vaccination of all girls against HPV.

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).

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