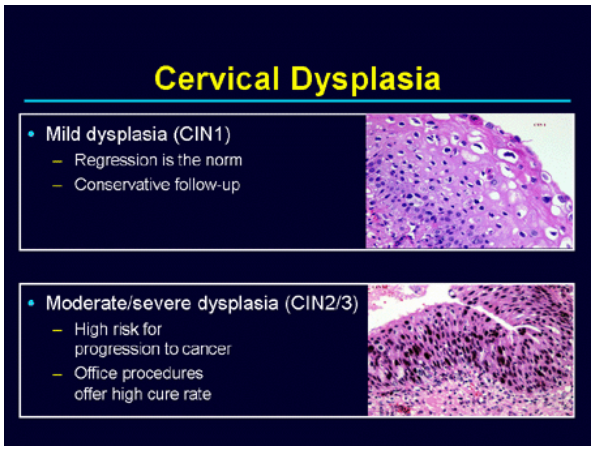
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet
on
Cervical Dysplasia

Introduction

Dysplasia (from Ancient Greek δυσ- *dys*-, 'bad' or 'difficult' and πλάσις *plasis*, 'formation') is an ambiguous term used in pathology to refer to an abnormality of development or an epithelial anomaly of growth and differentiation (epithelial dysplasia).



[Picture Credit: Cervical Dysplasia]

Epithelial dysplasia consists of an expansion of immature cells (such as cells of the ectoderm), with a corresponding decrease in the number and location of mature cells. Dysplasia is often indicative of an early neoplastic (cancerous) process. The term dysplasia is typically used when the cellular abnormality is restricted to the originating tissue, as in the case of an early, *in-situ* neoplasm.

Dysplasia, in which cell maturation and differentiation are delayed, can be contrasted with metaplasia, in which cells of one mature differentiated type are replaced by cells of another mature, differentiated type.

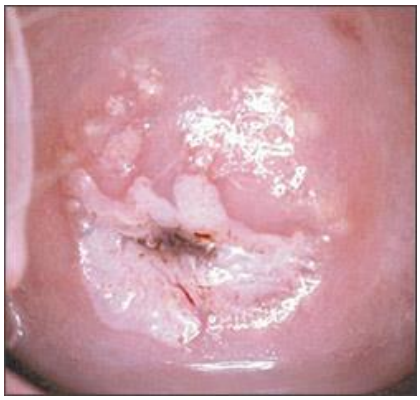
Examples of dysplasia include epithelial dysplasia of the cervix (cervical intraepithelial neoplasia – a disorder commonly detected by an abnormal Pap smear) consisting of an increased population of immature (basal-like) cells which are restricted to the mucosal surface, and have not invaded through the basement membrane to the deeper soft tissues. Analogous conditions include vaginal intraepithelial neoplasia and vulvar intraepithelial neoplasia.
(Wikipedia).

Cervical Dysplasia

Cervical dysplasia is not cancer. The term indicates that abnormal cells are found on the surface of the cervix.

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]

Cervical dysplasia can range from mild to severe, depending on the appearance of the abnormal cells. Dysplasia could go away on its own or, sometimes, it could develop into cancer. Another term for cervical dysplasia is cervical intraepithelial neoplasia.



[Picture Credit: Cervical Dysplasia 2]

After an abnormality is detected on a Pap smear, the doctor may recommend more tests, including:

- A Human Papilloma Virus (HPV) test
- Colposcopy.

Colposcopy is an examination of the cervix, vagina and vulva using a magnifying instrument. During a colposcopy, the doctor may determine where the abnormal cells are growing and the degree of abnormality. A sample of cells (biopsy) may be taken for testing.
(Mayo Clinic).

Colposcopy
Colposcopy (Ancient Greek: κόλπος *kolpos* "hollow, womb, vagina" + *skopos* "look at") is a medical diagnostic procedure to examine an illuminated, magnified view of the cervix and the tissues of the vagina and vulva. Many premalignant (precancerous) lesions and malignant (cancerous) lesions in these areas have discernible characteristics which can be detected through the examination.

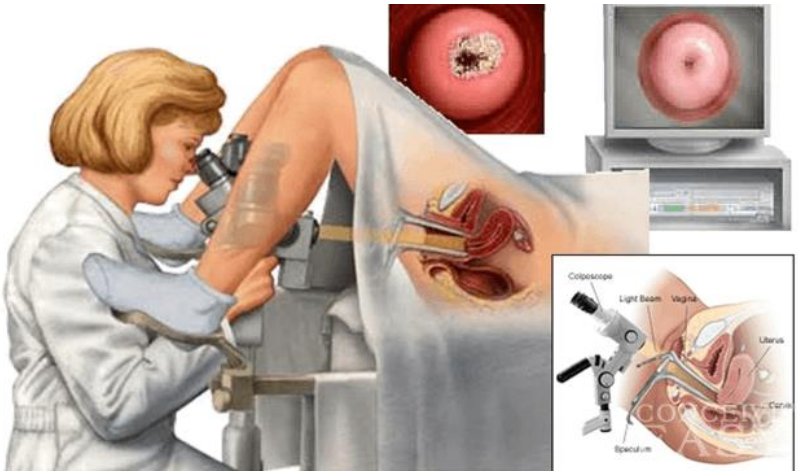
It is done using a colposcope, which provides an enlarged view of the areas, allowing the colposcopist (the person doing the examination) to visually distinguish normal from abnormal appearing tissue and take directed biopsies (small tissue samples) for further pathological examination. The main goal of colposcopy is to prevent cervical cancer by detecting precancerous lesions early and treating them.

The procedure (colposcopy) was developed by the German physician Hans Hinselmann, with help from Eduard Wirths.

Hans Hinselmann

Eduard Wirths

A specialised colposcope equipped with a camera is also used in examining and collecting evidence for victims of rape and sexual assault. (Wikipedia).



[Picture Credit: Colposcope]

Causes of Cervical Dysplasia

In many women with cervical dysplasia, Human Papilloma Virus (HPV) is found in cervical cells. HPV infection is common in women and men, and most often affects sexually active women under age 20.

In most cases, the immune system eliminates HPV and clears the infection. But in some women, the infection persists and leads to cervical dysplasia. Of the more than 100 different strains of HPV, more than one-third of them can be sexually transmitted, and two particular types - HPV 16 and HPV 18 - are strongly associated with cervical cancer.

HPV is usually passed from person to person during sexual contact such as vaginal intercourse, anal intercourse, or oral sex. But it also can be transmitted by any skin-to-skin contact with an infected person. Once established, the virus is capable of spreading from one part of the body to another, including to the cervix.

Among women with a chronic HPV infection, those women who smoke are twice as likely as non-smokers to develop severe cervical dysplasia because smoking suppresses the immune system.

Chronic HPV infection and cervical dysplasia are also associated with other factors that weaken the immune system, such as treatment with immunosuppressive drugs for certain diseases or after an organ transplant, or infection with HIV, the virus that causes AIDS. (WebMD).

Risk Factors for Cervical Dysplasia

There are several risk factors for cervical dysplasia, some of them directly related to the risk of HPV:

- having an illness that suppresses the immune system or being on immunosuppressant drugs
- having multiple sexual partners
- giving birth before the age of 16
- having sex before the age of 18
- smoking cigarettes
- having sex with an uncircumcised man
- Human papillomavirus (HPV) infection

- Genital warts
- History of one or more sexually transmitted diseases, such as genital herpes or HIV
- Having suppressed immune system, such as from HIV or chemotherapy to treat cancer
- Using birth control pills for longer than 5 years
- Being born to a mother who took diethylstilbestrol (DES) to become pregnant or to sustain pregnancy. This drug was used many years ago to promote pregnancy but it is no longer used for these purposes.
- Low levels of folate (vitamin B9) in red blood cells
- Dietary deficiencies in vitamin A, beta-carotene, selenium, vitamin E, and vitamin C (scientific data is not entirely conclusive at this time; see section on Nutrition and Dietary Supplements)

If one is sexually active, a condom might reduce the risk of getting HPV, but the virus can still live on the skin surrounding the genitals not covered by the condom.
(Healthline; WebMD; University of Maryland Medical Center).

A further risk factor for cervical dysplasia is the use of oral contraceptives - some research shows that women who use oral contraceptives may be at a higher risk for developing cervical dysplasia. However, it is not clear if the risk is directly attributable to the contraceptives themselves. One reason may be that oral contraceptives interfere with folic acid metabolism in the cells around the cervix, and folic acid may help prevent or improve cervical dysplasia. Another reason may be that women using this method of birth control may have increased exposure to sexually transmitted infections, compared to those who rely on a barrier method of contraception such as a condom.
(Health Communities).

Classification of Cervical Dysplasia
Cervical Dysplasia is classified as follows:

Cytologic analysis (screening tests) - Pap smear reports are based on a medical terminology system called The Bethesda System that was developed at the National Institutes of Health (NIH) in Bethesda, Maryland in 1988 and modified in 2001. The major categories for abnormal Pap smears reported in the Bethesda Systems are as follows:

ASC-US
This abbreviation stands for atypical squamous cells of undetermined significance. The word "squamous" describes the thin, flat cells that lie on the surface of the cervix. One of two choices are added at the end of ASC: ASC-US, which means undetermined significance, or ASC-H, which means cannot exclude HSIL (see below).

LSIL
This abbreviation stands for low-grade squamous intraepithelial lesion. This means changes characteristic of mild dysplasia are observed in the cervical cells.

HSIL
This abbreviation stands for high-grade squamous intraepithelial lesion. And refers to the fact that cells with a severe degree of dysplasia are seen.

Histologic analysis (cervical biopsies)
When precancerous changes are seen in tissue biopsies of the cervix, the term cervical intraepithelial neoplasia (CIN) is used. 'Intraepithelial' refers to the fact that the abnormal cells are present within the lining, or epithelial, tissue of the cervix. 'Neoplasia' refers to the abnormal growth of cells.

CIN is classified according to the extent to which the abnormal, or dysplastic, cells are seen in the cervical lining tissue:

CIN 1
Refers to the presence of dysplasia confined to the basal third of the cervical lining, or epithelium (formerly called mild dysplasia). This is considered to be a low-grade lesion.

CIN 2
Is considered to be a high-grade lesion. It refers to dysplastic cellular changes confined to the basal two-thirds of the lining tissue (formerly called moderate dysplasia).

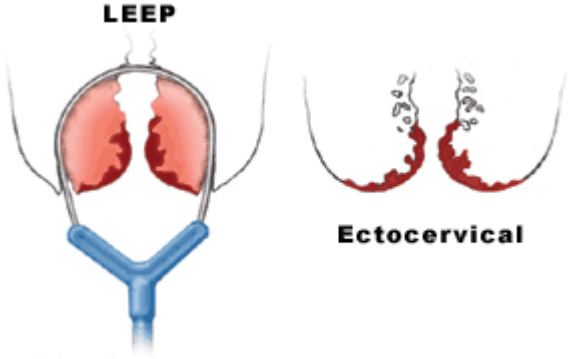
CIN 3
Is also a high grade lesion. It refers to precancerous changes in the cells encompassing greater than two-thirds of the cervical lining thickness, including full-thickness lesions that were formerly referred to as severe dysplasia and carcinoma in situ.
(MedicineNet.com).

Treatment of Cervical Dysplasia
Treatment of Cervical Dysplasia is as follows:

Surgical Treatments - If the doctor determines that someone has a high grade cervical lesion, he or she may advise the patient to have the lesion removed. The two most common methods of removing cervical lesions are by procedures called a **LEEP** or **Cold Knife Cone**. Both procedures are quick and typically have a quick recovery time.

The LEEP (Loop Electrosurgical Excision Procedure) can be performed either in the doctor's office or as an outpatient procedure in the operating room. The procedure starts much like a regular pelvic examination. The patient will need to lie down on an examining table and put her feet in the stirrups. Next, an instrument called a speculum is inserted into the vagina to hold the vaginal walls open so the physician can view the inside of the vaginal walls and the cervix.

A dilute vinegar solution is applied to the cervix to make the abnormal cells visible. An instrument called a colposcope will be used to visualise the cervix. The cervix is numbed with local anaesthesia. An electrically charged loop made of thin wire is inserted through the speculum and up to the cervix. As the loop is passed across the cervix, it cuts away a thin layer of surface tissue, removing the abnormal cells. This tissue is then sent to the laboratory to be tested for abnormal cells. In some instances, a medicated paste is applied to the area to prevent bleeding. If all of the abnormal cervical tissue is removed, no further surgery is needed, though abnormal cells may recur in the future.

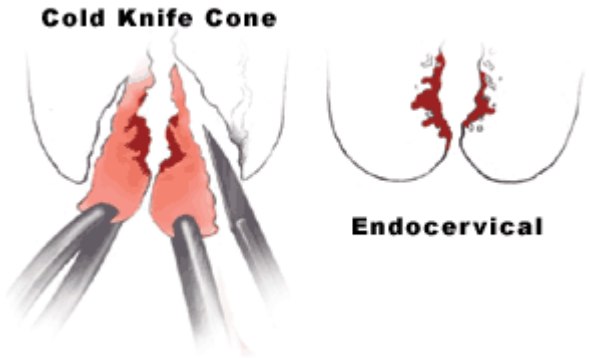


The doctor will give the patient instructions for recovering at home, including using pads to collect any discharge, avoiding strenuous activity for 48 hours, and abstaining from sexual intercourse for three to four weeks. The patient should also avoid tub baths, tampons or douching. Over the counter pain relievers can be used to relieve cramping.

Cold Knife Conisation is performed in the operating room, using a scalpel. The patient will be sedated using anaesthesia. She will lie on a table and place her feet in stirrups to position the pelvis for examination. An instrument called a speculum will be inserted into the vagina to hold the vaginal walls open so the physician can view the inside of the vaginal walls and the cervix.

The doctor will cut out a small, cone-shaped sample of tissue from the cervix. Pathologists will examine it under a microscope for any signs of cancer or abnormal cells. The procedure may be used to treat moderate to severe dysplasia (CIN II or III). Very early stage cervical cancer (stage 0 or IA1) may also be treated with this procedure. Abnormal cells from the cervical canal, including adenocarcinoma in situ, may be diagnosed, and sometimes treated with cold knife conisation.

Refer to the Fact Sheet on Cervical Cancer for additional information.



The doctor will give the patient instructions to prepare for the procedure and recover at home. Before the procedure, the patient may need to fast for six to eight hours. For two to three weeks after the procedure, she may have heavy, bloody, or a yellow-coloured discharge. She may experience some cramping or discomfort for a week or so. Avoid sexual intercourse, douching and use of tampons for about four to six weeks.
(Johns Hopkins Medicine).

Hysterectomy is the surgical removal of the uterus. Hysterectomy may be used if dysplasia recurs after any of the other treatment procedures.
(MedicineNet.com).

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	1:30	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.

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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