Cancer Association of South Africa (CANSA)

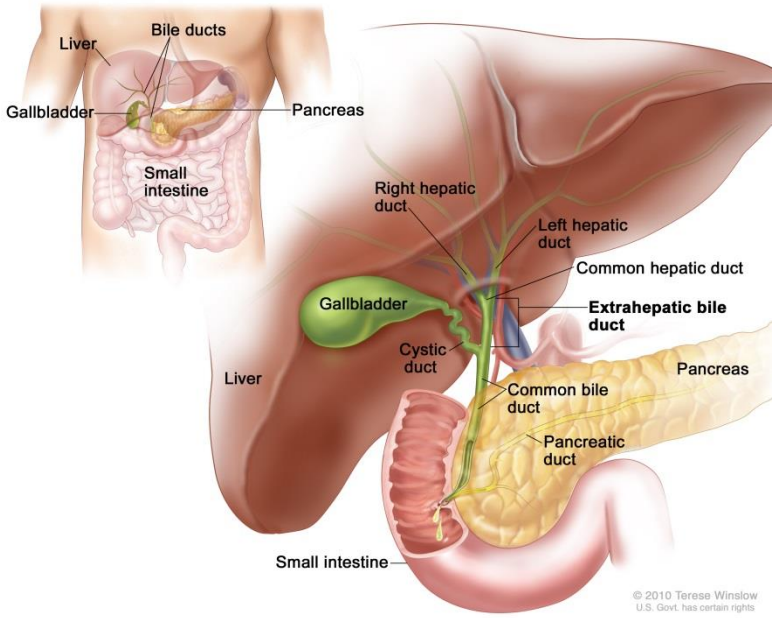
Research • Educate • Support

Fact Sheet on Bile Duct Cancer

Introduction

The biliary system consists of the organs and ducts (bile ducts, gallbladder, and associated structures) that are involved in the production and transportation of bile. The transportation of bile follows a particular sequence:

[Picture Credit: Biliary System]



- When the liver cells secrete bile, it is collected by a system of ducts that flow from the liver through the right and left hepatic ducts
- These ducts ultimately drain into the common hepatic duct
- The common hepatic duct then joins with the cystic duct from the gallbladder to form the common bile duct, which runs from the liver to the duodenum (the first section of the small intestine)
- Not all bile runs directly into the duodenum. About 50 percent of the bile produced by the liver is first stored in the gallbladder, a pear-shaped organ located directly below the liver
- When food is eaten, the gallbladder contracts and releases stored bile into the duodenum to help break down the fats

The biliary system's main function includes the following:

- To drain waste products from the liver into the duodenum
- To help in digestion with the controlled release of bile

Bile is the greenish-yellow fluid (consisting of waste products, cholesterol, and bile salts) that is secreted by the liver cells to perform two primary functions, including the following:

- To carry away waste
- To break down fats during digestion

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Bile salt is the actual component which helps break down and absorb fats. Bile, which is excreted from the body in the form of faeces, is what gives faeces its dark brown colour. (Ohio State University).

Bile Duct Cancer

Bile duct cancer (cholangiocarcinoma) is rare. It is almost always a type of cancer called adenocarcinoma, which starts in the lining of the bile duct. If cancer starts in the part of the bile ducts within the liver, it is known as intra-hepatic. If it starts in bile ducts outside the liver, it is known as extra-hepatic.

Incidence of Bile Duct Cancer

The National Cancer Registry (2012) does not furnish information regarding the incidence of bile duct cancer. According to the National Cancer Registry (2012) the following number of liver and bile duct cancer cases combined was histologically diagnosed in South Africa during 2012:

Group - Males 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	296	1:561	0,80%
Asian males	11	1:594	1,26%
Black males	185	1:600	1,58%
Coloured males	20	1:729	0,46%
White males	81	1:434	0,40%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	218	1:997	0,58%
Asian females	7	1:882	0,68%
Black females	125	1:1 139	0,76%
Coloured females	23	1:844	0,56%
White females	62	1:716	0,39%

The frequency of histologically diagnosed cases of liver and bile duct cancer in South Africa for 2012 was as follows (National Cancer Registry, 2012):

Group - Males 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	9	11	22	53	50	75	39	25
Asian males	0	0	0	2	0	4	2	1
Black males	9	7	15	34	36	34	18	10
Coloured males	0	2	1	4	3	4	5	0
White males	0	2	3	7	9	30	11	14

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	4	7	21	27	41	51	35	29
Asian females	0	0	1	2	1	3	0	0
Black females	3	4	16	16	23	24	20	10
Coloured females	0	1	0	6	5	5	4	1
White females	0	2	3	3	9	18	8	16

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Causes and Possible Risk Factors of Bile Duct Cancer
The cause of most bile duct cancers is unknown. There are a number of risk factors that can increase the risk of developing bile duct cancer. These include:

Inflammatory conditions - people who have a chronic inflammatory bowel condition, known as ulcerative colitis, have an increased risk of developing this type of cancer. People who have primary sclerosing cholangitis, which is an inflammatory condition that affects the bile ducts, are also at an increased risk of developing bile duct cancer.

Abnormal bile ducts - people who are born with (congenital) abnormalities of the bile ducts, such as choledochal cysts, have a higher risk of developing bile duct cancer. Choledochal cysts are congenital (present at birth) bile duct anomalies. These cystic dilatations of the biliary tree can involve the extrahepatic biliary radicles, the intrahepatic biliary radicles, or both.

Infection - in Africa and Asia, a large number of bile duct cancers are thought to be caused by infection with a parasite known as the liver fluke.

[Picture Credit: Liver Fluke]

Clonorchis sinensis is a human liver fluke found predominantly throughout China, Taiwan, Korea, Vietnam, and Japan. Commonly referred to as the Chinese liver fluke or Oriental liver fluke, this parasitic flatworm primarily targets humans as a definitive host, but a number of other animals are susceptible as well, including cats, dogs, pigs, rodents, foxes, badgers, and minks.

the human liver fluke does not reside in or upon its host's liver; rather, the parasite lives in the biliary (bile) ducts. Adult flukes generally measure 10 to 25 millimeters in length, and may live up to 10 years inside a host. The host is likely to be infected with numerous flukes, and cases are known where a single human host contained over twenty thousand of the parasites.

Increasing age - although bile duct cancers can occur in younger people, more than two out of three occur in people over 65.

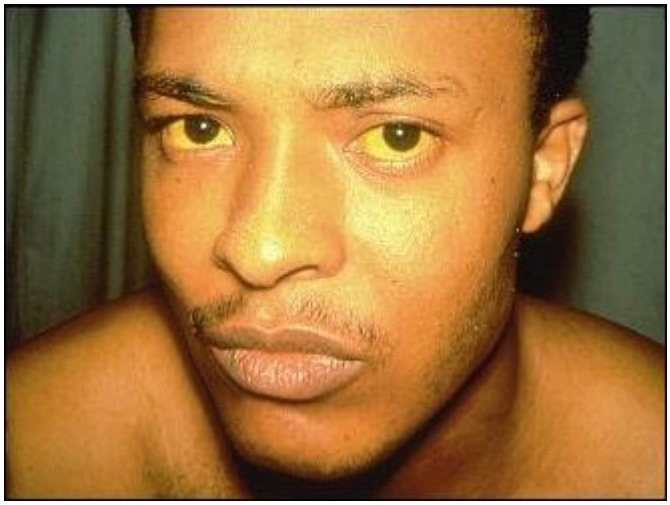
Bile duct cancer, like other cancers, is not infectious and cannot be passed on to other people.
(MacMillan Cancer Support; MicroscopyU)

Signs and Symptoms of Bile Duct Cancer
People with bile duct cancer may experience the following symptoms or signs, usually because the tumour is blocking the bile duct. Sometimes, people with bile duct cancer do not show any of these symptoms. These symptoms may also be caused by a medical condition that is not cancer.

One common symptom is jaundice, which is a yellowing of the skin and the whites of the eyes. When the bile duct is blocked, the liver cannot excrete bile, and the bile backs up into the bloodstream. The blockage may not be cancer; it can also be caused by a gallstone or

scar tissue. Bile contains bilirubin, which is dark yellow and can cause the skin and whites of the eyes to turn yellow if there are higher levels of it in the bloodstream. A person's urine may also become a dark colour, and bowel movements may become pale.

Jaundice is a common symptom for many conditions so there can be many causes. The doctor may need to do several diagnostic tests to find the exact cause. Many diseases associated with jaundice are not serious or life threatening and bile duct cancer is one of the less common causes.



[Picture Credit: Jaundice]

In addition to jaundice, other symptoms of bile duct cancer include:

- Itching, caused by a buildup of bile salts and bilirubin in the body that is then deposited in the skin
- Weight loss
- Loss of appetite
- Fever
- Abdominal pain. Early bile duct cancer usually does not cause pain, but a person may experience pain if the cancer has spread.

(Cancer.Net).

Diagnosis of Bile Duct Cancer

The following tests are commonly used to diagnose bile duct cancer:

Ultrasound Scan - This uses sound waves to make up a picture of the bile ducts and surrounding organs. One will usually be asked not to eat or drink anything for at least six hours before the scan. Once lying comfortably on one's back, a gel is spread on to the abdomen. A small device that produces sound waves is then rubbed over the area. The sound waves produce a picture on a computer. The test is painless and only takes a few minutes.

CT (Computerised Tomography) Scan - A CT scan takes a series of x-rays that build up a three-dimensional picture of the inside of the body. The scan is painless and takes 10-30 minutes. CT scans use small amounts of radiation, which is very unlikely to hurt one or anyone one comes in contact with. The patient will be asked not to eat or drink for at least four hours before the scan.

The patient may be given a drink or injection of a dye that allows particular areas to be seen more clearly. This may make one feel hot all over for a few minutes. If allergic to iodine or have asthma, one could have a more serious reaction to the injection, so it is important to let the treating doctor know beforehand.

Spiral CT scan - In this test, the X-ray machine rotates continuously around the body to make cross-sectional pictures.

MRI (Magnetic Resonance Imaging) Scan - This test is similar to a CT scan but uses magnetism, instead of X-rays, to build up a detailed picture of areas of the body. Before the scan the patient may be asked to complete and sign a checklist. This is to make sure it is safe for the particular patient to have an MRI scan.

Before having the scan, the patient will be asked to remove any metal belongings, including jewellery. Some people are given an injection of dye into a vein in the arm. This is called a contrast medium and can help images from the scan show up more clearly. During the test the patient will be asked to lie very still on a couch inside a long cylinder (tube) for about 30 minutes. It is painless but can be slightly uncomfortable, and some people feel a bit claustrophobic during the scan. It is also noisy, but one will be given earplugs or headphones. The patient will be able to hear, and speak to, the person operating the scanner.

ERCP (Endoscopic Retrograde Cholangio-Pancreatography) - This procedure may be used to take an X-ray picture of the pancreatic and bile ducts. It may also be used to unblock the bile duct, if necessary.

One's stomach and the first part of one's small bowel (duodenum) need to be empty for this test. So one will be asked not to eat or drink anything for about six hours beforehand.

The patient is given an injection to relax (a sedative) and a local anaesthetic spray to numb the throat. The doctor passes a thin, flexible tube called an endoscope into the mouth, down to the stomach and into the duodenum (small bowel).

The doctor looks down the endoscope to find the opening where the bile duct and pancreatic duct drain into the duodenum. He/she may then inject a dye, which shows up on X-ray, into these ducts. This helps to show if there is any abnormality or blockage in the ducts.

If there is a blockage, the doctor may insert a small tube known as a stent. The patient will be given antibiotics beforehand to help prevent any infection and will probably stay in hospital overnight.

Endoscopic Ultrasound Scan (EUS) - This scan is similar to an ERCP, but involves an ultrasound probe being passed down the endoscope to take an ultrasound scan of the bile ducts and surrounding structures.

PTC (Percutaneous Transhepatic Cholangiography) - This procedure may be used to take an x-ray picture of the bile duct. It may also be used to get a sample of tissue (biopsy) from the tumour. The patient will be asked not to eat or drink anything for about six hours before the test and will be given a sedative just like with an ERCP.

The doctor will numb an area on the right side of the tummy (abdomen) with a local anaesthetic injection. He/she will then pass a thin needle through the skin into the liver and inject a dye into the bile duct within the liver. X-rays will be taken to see if there is any abnormality or blockage of the duct.

One may feel some discomfort as the needle enters the liver. The patient will be given antibiotics before and after the procedure to help prevent infection, and will stay in hospital for at least one night afterwards.

Angiogram - This is a test to look at blood vessels. The bile duct is very close to large blood vessels, which carry blood to and from the liver. An angiogram may be used to check whether any of them are affected by the cancer.

Angiograms are carried out in the X-ray department. A fine tube is put into a blood vessel (artery) in the groin. A dye is then injected up the tube. The dye circulates in the arteries so that they show up on X-ray.

Biopsy - The results of the previous tests may make the doctor strongly suspect that one have cancer of the bile duct, but the only way to be sure is by having a biopsy. Some cells or tissue samples are taken from the affected area of the bile duct. The biopsy sample is then looked at under a microscope. A biopsy may be carried out during an ERCP or PTC.

CT or ultrasound may be used at the same time to make sure the biopsy is taken from the right place.

Laparotomy - An operation called a laparotomy is sometimes used to help diagnose bile duct cancer. The operation is carried out under a general anaesthetic so the patient is not awake.

The surgeon makes a cut (incision) in the abdomen to examine the bile duct and the tissue around it for cancer. A tube with a tiny camera attached called a laparoscope helps the surgeon see inside the abdomen.

If a cancer is found, but looks as though it has not spread to surrounding tissues, the surgeon may be able to remove the cancer or relieve any blockage that it is causing.
(MacMillan Cancer Support; New York Presbyterian).

Staging of Bile Duct Cancer
Staging is the process of finding out how far a cancer has spread. The stage (extent) of bile duct cancer is one of the most important factors in selecting treatment options and estimating a patient's outlook for recovery and outlook (prognosis).

A staging system is a standardised way for members of the cancer care team to summarise the extent of a cancer's spread. The stage of a cancer is determined by the results of the physical examination, testing (such as imaging and other tests), and by the results of surgery if it has been done.

The major system used to describe the stages of bile duct cancer is the American Joint Committee on Cancer (AJCC) TNM system. There are actually 3 different staging systems for bile duct cancers, depending on where it starts.

Intrahepatic bile duct cancers (those starting within the liver) are staged separately from extrahepatic bile duct cancers. Also, extrahepatic bile duct cancers are split into two (2) groups: perihilar tumours (also called a Klatskin tumour, begins where many small channels

join into the bile duct at the point where it leaves the liver) and distal tumours. The TNM system for all bile duct cancers contains three (3) key pieces of information:

- **T** describes whether the main tumour has invaded through the wall of the bile duct and whether it has invaded other nearby organs or tissues.
- **N** describes whether the cancer spread to nearby (regional) lymph nodes (bean-sized collections of immune system cells located throughout the body).
- **M** indicates whether the cancer has metastasized (spread) to other organs of the body. (The most common sites of bile duct cancer spread are the liver, peritoneum [the lining of the abdominal cavity], and the lungs.)

Numbers or letters appear after T, N, and M to provide more details about each of these factors:

- The numbers 0 through 4 indicate increasing severity
- The letter X means "cannot be assessed" because the information is not available

The TNM system divides bile duct cancers into several groups that help give doctors an idea about a person's prognosis (outlook). But for treatment purposes, doctors often use a simpler system based on whether these cancers are likely to be resectable (able to be completely removed by surgery) or unresectable. In general terms, most stage III and IV tumours are unresectable, but there may be exceptions. Resectability is based on the size and location of the tumour, how far it has spread, and whether or not a person is healthy enough to have surgery.
(American Cancer Society).

Treatment of Bile Duct Cancer

The main treatment for bile duct cancer is surgery. But surgery is not always possible. Many cancers of the bile duct are diagnosed when they are already advanced. If the surgeon cannot remove the tumour the patient may have radiotherapy, or chemotherapy, or both. This will help to control the cancer and its symptoms.

The treatment will depend on

- Where the cancer is in the bile duct
- The size of the tumour
- Whether it has spread to other parts of the body (the stage)
- The patient's general health

<u>Surgery for bile duct cancer</u>

The type of surgery depends on where the cancer is in the bile duct. It also depends on whether it has spread into other nearby organs. Any surgery for bile duct cancer is a major operation.

The patient may have:

- Removal of the bile duct
- Removal of the bile duct and part of the liver
- Whipple's operation - in the Whipple operation the head of the pancreas, a portion of the bile duct, the gallbladder and the duodenum is removed. Occasionally a portion of the stomach may also be removed. After removal of these structures the remaining

pancreas, bile duct and the intestine is sutured back into the intestine to direct the gastrointestinal secretions back into the gut.

Removal of the bile duct - if the tumour is at an early stage (stage 1) it may be possible for the surgeon to just remove the bile duct.

Removal of the bile duct and part of the liver - if the tumour is in the bile ducts within the liver (intrahepatic) or is a perihilar tumour, the patient will need to have part of the liver removed. The patient may also have the nearby lymph nodes removed. The surgeon joins the bile duct to the small bowel. The liver usually recovers well afterwards.

The patient will need to be in intensive care for a few days afterwards and will have to stay in hospital for at least 2 weeks.
(Cancer Research UK).

Unresectable (cancers that cannot be operated) bile duct cancers - This includes most stage III and IV cancers, as well as some earlier stage cancers if a person is not healthy enough for surgery.

If it's not clear if a cancer is resectable, chemotherapy and/or radiation therapy may be used first to try to shrink the cancer and make it resectable. Surgery could then be done to try to remove the cancer completely.

In some cases, the doctor might think that a cancer is resectable, but once the operation starts it becomes clear that it cannot be removed completely. For example, the cancer may turn out to be larger or have spread farther than was visible on imaging tests before surgery. At this point it would not usually be helpful to remove only part of the cancer, but the surgeon may do a biliary bypass at this time to relieve any bile duct blockage or to try to prevent it from becoming a problem in the future. Placing stents in the bile duct to keep it open may also be an option during surgery.

For some unresectable intrahepatic or perihilar bile duct cancers, a liver transplant (after complete removal of the liver and bile duct) may be an option.

Chemotherapy and radiation therapy may be given first. Although, it is often hard to find a compatible liver donor, a liver transplant can provide a chance for a cure.

For other bile duct cancers that are clearly not resectable (based on the results of imaging tests and/or laparoscopy), treatment is aimed at trying to control the growth of the cancer and to keep symptoms to a minimum for as long as possible.

Radiation therapy and/or chemotherapy may shrink or slow the growth of the cancer for a time. When chemotherapy is given alone (without radiation) the drugs cisplatin and gemcitabine (Gemzar) are often used. When chemotherapy is given with radiation therapy, the drug 5-FU is most often used. For bile duct cancers within the liver, ablation using extreme heat (radiofrequency ablation) or cold (cryotherapy) may help control the tumours. Unfortunately, almost all cancers begin to grow again eventually. For people looking to continue to try to treat the cancer, taking part in clinical trials of newer treatments may be an option.

Much of the focus of treating people with unresectable cancers is on relieving symptoms from the cancer. Two of the most important problems are bile duct blockage (which can lead to jaundice, itching, and other symptoms) and pain.

Bile duct blockage can be treated (and in some cases prevented) with surgery or other procedures. In most people with unresectable cancer, it is probably best to avoid a major operation if it can be helped. A biliary bypass may be a good option if a patient is already having surgery and the cancer turns out to be unresectable. In other cases, a stent or catheter may be placed in the bile duct to keep it open or allow it to drain. This can be done by placing a needle through the skin above the liver (percutaneously) or using an endoscope (an instrument used to look inside the body) passed down the mouth. It can also be done surgically in some cases.

Other options to help keep the bile duct open include brachytherapy (placing a tube with radioactive pellets inside the bile duct for a short time) and photodynamic therapy (injecting a light-sensitive drug into the blood and then using an endoscope with a special light on the end inside the bile duct).

Advanced bile duct cancer may be painful, so it is important to tell the doctor about any pain right away so it can be managed effectively. Radiation therapy, alcohol injection, and ablation of tumours within the liver can be used to relieve pain in some cases. Doctors often prescribe opioid pain-killing drugs (like morphine) as needed. Some patients may hesitate to use opioid drugs for fear of becoming addicted to them. Yet some of the most effective pain-killing drugs are opioids, and studies show that most patients are not at risk of becoming addicted to drugs prescribed for them to stop pain for medical conditions.

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard

treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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