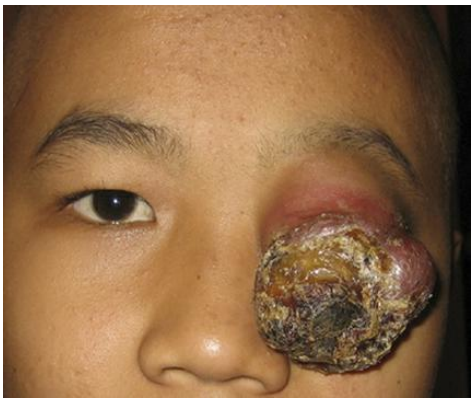
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Adult Rhabdomyosarcoma and Pleomorphic Rhabdomyosarcoma

Introduction

Sarcomas are cancers that develop from connective tissues in the body, such as muscles, fat, bones, the linings of joints, or blood vessels. There are many types of sarcomas.



[Picture Credit: Rhabdomyosarcoma]

Rhabdomyosarcoma (RMS) is a cancer made up of cells that normally develop into skeletal muscles. The body has 3 main types of muscles.

- Skeletal (voluntary) muscles are muscles that we control to move parts of our body.
- Smooth muscle is the main type of muscle in internal organs (except for the heart). For example, smooth muscles in the stomach and intestines push food along as it is digested. We do not control this movement.
- Cardiac muscle is the main muscle type in the heart.

About 7 weeks into the development of an embryo, cells called *rhabdomyoblasts* (which will eventually form skeletal muscles) begin to form. These are the cells that can develop into RMS. Because this is a cancer of embryonal cells, it is much more common in children, although it does sometimes occur in adults – more than 50% of cases are diagnosed before the age of 10.
(American Cancer Society).

Incidence of Rhabdomyosarcoma in South Africa

The National Cancer Registry does not provide any information regarding the incidence of Rhabdomyosarcoma in South Africa.

Rhabdomyosarcoma in Adults

Rhabdomyosarcoma (RMS) is a paediatric sarcoma rarely occurring in adults. Greater than 50% of cases are diagnosed before the age of 10. Males are affected slightly more than females. For unknown reasons, adults with RMS have worse outcomes.

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; Dip Genetic Counselling; Diagnostic Radiographer; Dip Audiometry and Noise Measurement]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Rhabdomyosarcoma is very uncommon in adults. There have been five "large" published series, totalling just over 400 cases of "adult" RMS (including some "children") seen at major cancer centres in the United States and Europe over the past 20-30 years. Although "pleomorphic" histology is more common in the adult population (and rarely seen in children), treatment principles for managing adults with RMS are similar to those for children, and outcome is not intrinsically worse for adults treated with "modern", multi-modality therapy.

Rhabdomyosarcomas can occur anywhere in the body but occur more commonly near muscular structures – e.g., around the intestines, around the ocular muscles and in the cardiac muscle in tuberous sclerosis. The most common locations of rhabdomyosarcomas are:

- Head and neck (35-40%).
- Bladder (20%).
- Muscles, limbs, chest and abdominal wall (15-20%).
- Other sites – e.g., testes.

Rhabdomyosarcomas are highly malignant and grow rapidly. They are, however, potentially curable now.
(The Liddy Shriver Sarcoma Initiative; Sarcoma Foundation of America; Patient.info).

Epidemiology
Prognosis for most of those diagnosed with rhabdomyosarcoma has improved significantly in the last 30 years. Overall survival rates have improved from 25% to more than 70% in recent reports.

Prognosis is influenced by the primary site of disease, the extent of disease and the histologic subtype. Favourable primary sites include the orbit, the head and neck region (except the areas near the lining of the nervous system), the vagina and the area near the testis.

The extent of the disease, particularly after surgery, is also important. Those who have surgery which completely or almost completely removes all tumours have a better outlook than those who have significant disease remaining after surgery.

Most rhabdomyosarcomas occur without predisposing risk factors. In some cases these tumours are associated with a genetic predisposition to cancer such as the Li-Fraumeni syndrome. Rhabdomyosarcoma can involve regional lymph nodes at a higher rate than other soft tissue sarcomas, and this can impact on prognosis as well. With regard to histology, embryonal rhabdomyosarcoma has a more favourable prognosis than the alveolar subtype.
(Sarcoma Foundation of America).

Contributory Causes of Rhabdomyosarcoma (RMS)
The exact causes of Rhabdomyosarcoma remains unclear, although genetic syndromes and various other factors are associated with this condition. Factors that are associated with Rhabdomyosarcoma include:

- Smoking – This is included in our Risk Factors because most of the cancers are induced by smoking.
- Radiation – This can cause a change or mutation in normal cells
- Drug Abuse – studies have shown that the use of illegal drugs are connected with adults who have Rhabdomyosarcoma

(CancerWall.Com).

Adult Rhabdomyosarcoma

Rhabdomyosarcoma is rare in adults. The most common subtype of rhabdomyosarcoma to occur in adults, however, is the pleomorphic type (PRMS).

Other rhabdomyosarcoma subtypes that occur in adults include:

- predominantly juvenile alveolar rhabdomyosarcoma subtype
- embryonal Rhabdomyosarcoma
- spindle cell rhabdomyosarcoma subtype of embryonal
- rare adult clear cell rhabdomyosarcoma
- sclerosing pseudovascular rhabdomyosarcoma subtype

Several studies have addressed PRMS during the past two decades using immunohisto-chemical techniques, but only on small numbers of tumours. The latest cytoskeletal and noncytoskeletal muscle markers have not yet been fully explored in these tumours.

Morphologic Variants of Pleomorphic Rhabdomyosarcoma (PRMS)

Type	Morphology
Classic PRMS	Sheets of large atypical, polygonal pleomorphic rhabdomyoblasts with abundant eosinophilic cytoplasm (PRMB)
Round-cell PRMS	Clusters of PRMB; medium sized, slightly pleomorphic, round RMB in background; no areas of true embryonal RMS
Spindle-cell PRMS	Scattered PRMB; MFH-like spindled background of RMB

RMB, rhabdomyoblasts; RMS, rhabdomyosarcoma; MFH, malignant fibrous histiocytoma.
(Modern Pathology).

Staging and Prognosis

Staging of RMS is determined by the tumour size and local invasion, lymph nodes involvement, and metastasis, all of these are basically seen in the preoperative work up and physical exam. The table below shows the pre-treatment TNM staging system for RMS.

Pretreatment TNM staging system for RMS

Stage	Sites	T	Size	N	M
1	Orbit, head, and neck (excluding parameningeal), genitourinary (nonbladder/nonprostate), billary tract	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Bladder/prostate, extremity, cranial, parameningeal, other (includes trunk, retroperitoneum, etc.)	T1 or T2	a	N0 or Nx	M0
3	Bladder/prostate, extremity, cranial, parameningeal, other (includes trunk, retroperitoneum, etc.)	T1 or T2	a	N1	M0
			b	N0 or N1 or NX	M0
4	Any	T1 or T2	a or b	N0 or N1	M1

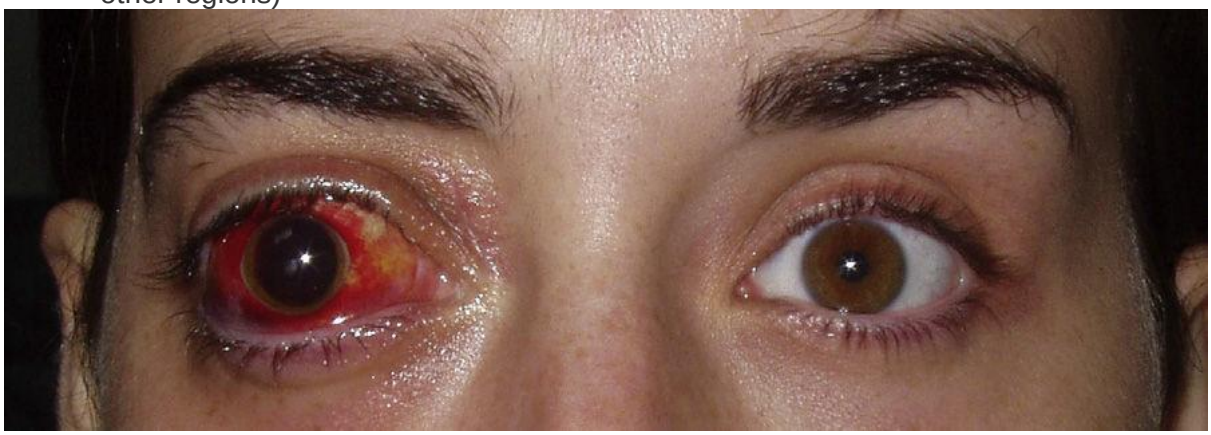
Size a, ≤5 cm in diameter; b, >5 cm in diameter

(Link.Springer).

Pleomorphic Rhabdomyosarcoma

Pleomorphic Rhabdomyosarcoma (PRMS) is an extremely infrequent, but highly malignant 'skeletal muscle' tumour of the soft tissues.

- It is composed of an unusual mix of round, spindle, and polygonal-shaped cells seen with differentiated skeletal muscles. It may develop deep within the body tissues
- Middle-aged adults are affected by these soft tissue sarcomas
- The regular locations for PRMS are the lower and upper limbs. Other not so frequent locations include the chest and abdomen
- Treatment includes surgical removal of the tumour with radiation & chemotherapy; nevertheless, the long-term outcome is grim (especially if the tumour spreads to other regions)



[Picture Credit: Adult Orbital Alveolar Pleomorphic Rhabdomyosarcoma]

Incidence of Pleomorphic Rhabdomyosarcoma

- Even though Pleomorphic Rhabdomyosarcoma is observed across all ages; a majority of them are noticed in adults over 40 years, with a peak in the 50-60 year age range. Young children are hardly affected

- Males are affected more than females
- There is no ethnic/racial preference noticed

Risk Factors for Pleomorphic Rhabdomyosarcoma

The risk is thought to be linked to inherited genetic defects, or to those defects that develop spontaneously. The body physiological conditions, a regular lifestyle, or environmental factors, do not play any role in Pleomorphic Rhabdomyosarcoma development.

It is important to note that having a risk factor does not mean that one will get the condition. A risk factor increases ones chances of getting a condition compared to an individual without the risk factors. Some risk factors are more important than others.

Also, not having a risk factor does not mean that an individual will not get the condition. It is always important to discuss the effect of risk factors with your healthcare provider.

Causes of Pleomorphic Rhabdomyosarcoma

- The cause and mechanism of Pleomorphic Rhabdomyosarcoma formation is unknown
- The rapidly forming and acutely infiltrative tumour is said to arise from embryonic connective tissues responsible for skeletal muscle development
- It is suspected that either inherited genetic defects or de novo (sporadic and spontaneous) genetic mutations may be the causative agents. Some random mutations of chromosomal anomalies/irregularities have been recorded

Signs and Symptoms of Pleomorphic Rhabdomyosarcoma

The presentations are based on the location of PRMS. Signs and symptoms of Pleomorphic Rhabdomyosarcoma include:

- In the initial growing phase of the tumours, they are normally asymptomatic
- As the tumour grows rapidly, its presence is felt by pain and a sensation of mass. The mass can cause compression on the body region, resulting in obstruction of adjacent organs
- Most lesions occur in the legs (in 45% of the cases) followed by the hands. Occasionally, it is found in the abdomen and on the chest wall too
- Functional impairment of organs may occur owing to the large size of the tumour (5-15cm), due to mass effect

Diagnosis of Pleomorphic Rhabdomyosarcoma

Pleomorphic Rhabdomyosarcoma is diagnosed by:

- Physical examination, evaluation of patient's medical history
- Histopathological studies conducted on a biopsy specimen
- Ultrasonography the of affected region
- CT, MRI scan of the affected region
- Whole-body PET scan, bone scan of the affected region to check for tumour metastasis. This helps with staging of the tumour

Possible Complications of Pleomorphic Rhabdomyosarcoma

Complications from Pleomorphic Rhabdomyosarcoma could include:

- Complications are dependent on the site and stage of the tumour. It is easier to treat the primary tumour; but if metastasis occurs, treatment can be challenging
- Metastasis may occur within 12-15 months of tumour growth; the metastasis rate is around 55%
- Recurrence of the tumour post-surgery; recurrence rate is 45% and often happens within a year of surgical excision of the primary tumour
- Damage to vital nerves, blood vessels, and surrounding structures during surgery
- Side effects from chemotherapy (such as toxicity), radiation therapy (radiation fibrosis)

Treatment of Pleomorphic Rhabdomyosarcoma

Treatment measures for Pleomorphic Rhabdomyosarcoma include the following:

- Wide surgical excision of PRMS with removal of the entire lesion; this is essentially followed by radiation and/or intensive chemotherapy
- If possible, sometimes chemotherapy/radiotherapy is given prior to the operation, to shrink the tumour
- Arterial embolization of the tumour is used to provide temporary relief from the symptoms, and reduce blood loss during 'tumour removal' surgical procedure
- When PRMS is at an inaccessible location, or is unsafe for a surgical intervention; non-invasive procedures are adopted
- Post-operative care is important: Minimum activity level is to be ensured until the surgical wound heals. Follow-up care with regular screening and check-ups are important

Reducing the Risk of Pleomorphic Rhabdomyosarcoma

- Current medical research have not established a way of preventing Pleomorphic Rhabdomyosarcoma
- Genetic counselling and testing: If there is a family history of the condition, then genetic counselling will help assess risks, before planning for a child
- The presence of any tumour or lesion should be immediately informed to the physician
- Regular medical screening at periodic intervals with blood tests, scans, and physical examinations are mandatory for those who have already endured PRMS; due to its high metastasizing potential and chances of recurrence. Often several years of active vigilance is necessary

Prognosis of Pleomorphic Rhabdomyosarcoma

- Pleomorphic Rhabdomyosarcomas are rare, but highly malignant cancers
- A set of reliable factors for PRMS prognosis have not yet been developed. However, the long-term outcome may depend on a combination of factors such as; age of the

individual, tumour stage at detection, size, type, and location of the tumour, and whether it has spread around the area, or to other distant regions
- The long-term outcome is poor with metastases for most individuals (with a 30% survival rate)

(DoveMed).

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.

<u>Use of Placebos</u>
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.

Whilst CANSA has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

Sources and References

Adult Orbital Alveolar Pleomorphic Rhabdomyosarcoma
http://www.elsevier.es/en-revista-archivos-sociedad-espanola-oftalmologia-english-496-articulo-orbital-alveolar-rhabdomyosarcoma-masked-by-S2173579414001108

American Cancer Society
https://www.cancer.org/cancer/rhabdomyosarcoma/about/what-is-rhabdomyosarcoma.html

CancerWall.Com
https://cancerwall.com/rhabdomyosarcoma-symptoms-survival-rate-prognosis-picture/

DoveMed
http://www.dovemed.com/diseases-conditions/pleomorphic-rhabdomyosarcoma-prms/

Link.Springer
https://link.springer.com/article/10.1007%2Fs11864-015-0342-8

Modern Pathology
http://www.nature.com/modpathol/journal/v14/n6/full/3880357a.html

National Cancer Institute
http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials

Patient.info
https://patient.info/doctor/rhabdomyosarcoma-pro

Rhabdomyosarcoma
https://cancerwall.com/rhabdomyosarcoma-symptoms-survival-rate-prognosis-picture/

Sarcoma Foundation of America
http://www.curesarcoma.org/patient-resources/sarcoma-subtypes/rhabdomyosarcoma/

The Liddy Shriver Sarcoma Initiative
http://sarcomahelp.org/rhabdomyosarcoma.html