Cancer Association of South Africa (CANSA)

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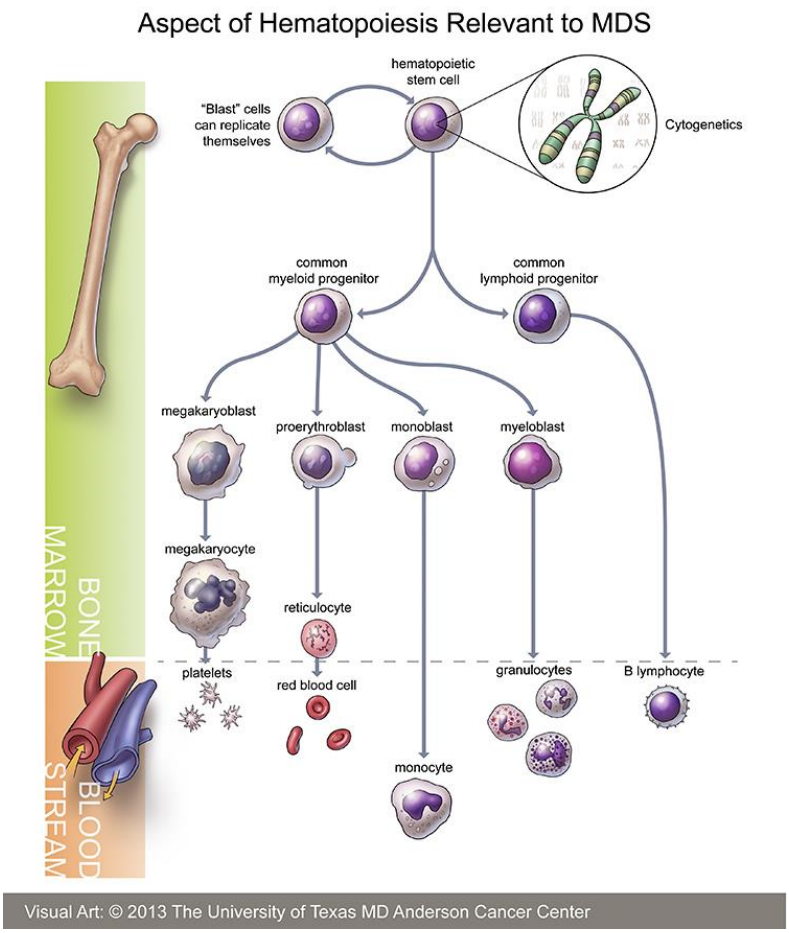
Fact Sheet on Myelodysplastic Syndromes

Introduction

Myelodysplastic syndromes (MDS) are a group of diseases that affect normal blood cell production in the bone marrow. In MDS the bone marrow produces abnormal, immature blood cells called *blast cells*. These cells fail to mature properly and are unable to work adequately. They often die before they leave the bone marrow, or shortly after reaching the bloodstream. Without enough normal cells being produced by the bone marrow (red cells, white cells and platelets) people with MDS can become fatigued, more susceptible to infections, and to bleeding and bruising more easily.



[Picture Credit: Haematopoiesis]

MDS is a collection of heterogeneous haematopoietic disorders. The disorders that belong to this group are characterised by either a hypo-cellular (low) or hyper-cellular (high) marrow with its maturation and morphology impaired. Simply put, they are conditions that have resulted due to ineffective production of blood cells in the bone marrow.

There are seven (7) different types of MDS and the disease can vary in its severity and the degree to which normal blood cell production is affected. About 30% of people with MDS will progress to acute myeloid leukaemia (AML). MDS is sometimes referred to as a *pre-leukaemic* disorder.

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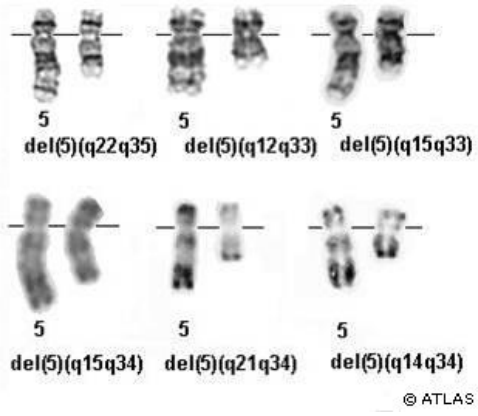
According to the World Health Organization classification there are seven (7) types of MDS. They include:

- Refractory cytopaenia with unilineage dysplasia (RCUD) - About 5% to 10% of all MDS patients have RCUD. People with RCUD have low numbers of one type of blood cell, but normal numbers of the other 2 types.
- Refractory anaemia with ringed sideroblasts (RARS) - About 10% to 15% of all people with MDS have this type. This condition is similar to refractory anaemia - the patient has low numbers of red blood cells but normal numbers of white blood cells and platelets.
- Refractory cytopaenia with multilineage dysplasia (RCMD) - About 40% of people with MDS have this type. In this condition, the counts of at least 2 types of blood cells are low.
- Refractory anaemia with excess blasts-1 (RAEB-1) - One or more cell types are low in the blood and look abnormal in the bone marrow. The number of blasts in the bone marrow is increased; but is still less than 10%.
- Refractory anaemia with excess blasts-2 (RAEB-2) - This type of MDS is similar to RAEB-1 except the bone marrow contains more blasts – between 10% and 20% of the bone marrow cells are blasts. The blood also contains more blasts.
- Myelodysplastic syndrome, unclassified (MDS-U) - This type of MDS is uncommon. For a case to be considered MDS-U, the findings in the blood and bone marrow cannot fit any other type of MDS.
- Myelodysplastic syndrome associated with isolated del(5q) - In this type of MDS, the chromosomes of the bone marrow cells are normal except they show that a part of chromosome number 5 is missing. In the blood, the red cell counts are low, but the white blood cell counts are normal. Often the platelet count is increased.

[Picture Credit: Del(5q)]



Dao, K.T. 2017. Myelodysplasctic syndromes: updates and nuances.
"Myelodysplastic syndrome (MDS) is a heterogeneous, clonal stem cell disorder of the blood and marrow typically diagnosed based on the presence of persistent cytopenia(s), dysplastic cells, and genetic markers. Common issues that arise in the clinical management include difficulty confirming MDS diagnosis, lack of a standard approach with novel agents in MDS, and few prospective long-term, randomized controlled MDS clinical studies to guide allogeneic blood and marrow transplant. With the recent genetic characterization of MDS, certain aspects of these issues will be better addressed by integrating genetic data into clinical study design and clinical practice."

Incidence of Myelodysplastic Syndrome (MDS) in South Africa

Because Myelodysplastic Syndrome is a pre-leukaemia condition, the National Cancer Registry (2017) does not provide any information about the incidence of this condition.

Causes of Myelodysplastic Syndrome (MDS)
The risks of MDS increase with age. Factors that raise your risk of these problems include:

Cancer therapy - the use of certain chemotherapy drugs used in the treatment of cancer plays a role in some cases of myelodysplastic syndrome. MDS may be more likely to occur after treatment for acute lymphocytic leukaemia in childhood, Hodgkin's lymphoma, or non-Hodgkin's lymphoma.

Cancer drugs linked to myelodysplastic syndrome include:

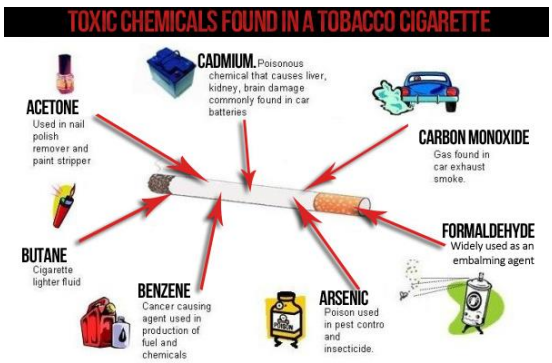
- Leukeran (chlorambucil)
- Cytoxan (cyclophosphamide)
- Adriamycin (doxorubicin)
- Etopophos (etoposide)
- Ifex (ifosfamide)
- Mustargen (mechlorethamine)
- Alkeran (melphalan)
- Matulane (procarbazine)
- Vumon (teniposide)

Some inherited conditions may raise someone's risk of having myelodysplastic syndrome. These include:

- Fanconi anaemia - in this condition, the bone marrow fails to make sufficient amounts of all three types of blood cells.
- Shwachman-Diamond syndrome - tis keeps the bone marrow from making enough white blood cells.
- Severe congenital neutropenia.- this condition is marked by insufficient neutrophils, which are a type of white blood cell.

Other causes of myelodysplastic syndromes:

- Exposure to chemicals - one may be more likely to develop myelodysplastic syndrome following long-term workplace exposure to benzene and other chemicals used in the petroleum and rubber industries.
- Smoking also raises the risk of MDS.
- Radiation – gamma rays and X-rays.
- Pesticides
- Heavy metals – lead and mercury



[Picture Credit: Smoking]

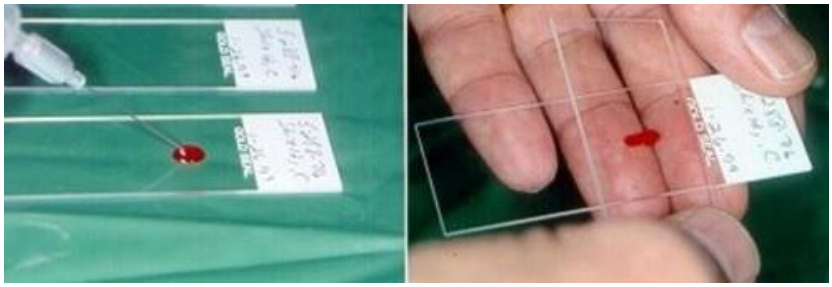
Signs and Symptoms of Myelodysplastic Syndrome (MDS)
People with MDS may experience one or more of the following symptoms or signs. Sometimes, people with MDS do not show any of these symptoms. Or, these symptoms may be caused by a medical condition that is not MDS. If concerned about a symptom or sign on this list, please talk with a medical doctor.

- Fatigue

- Weakness
- Unusual paleness 9pallor) due to anaemia
- Easy bruising or bleeding
- Pinpoint-sized red spots just beneath the skin caused by bleeding (petechiae)
- Fever
- Bone pain
- Shortness of breath
- Frequent infections

Diagnosis of Myelodysplastic Syndrome (MDS)
If signs and symptoms suggest a patient may have MDS, the doctors will usually look at cells from the blood and bone marrow to confirm this diagnosis.

Blood cell counts and blood cell examination - the complete blood count (CBC) is a test that measures the different cells in the blood, such as the red blood cells, the white blood cells, and the platelets.



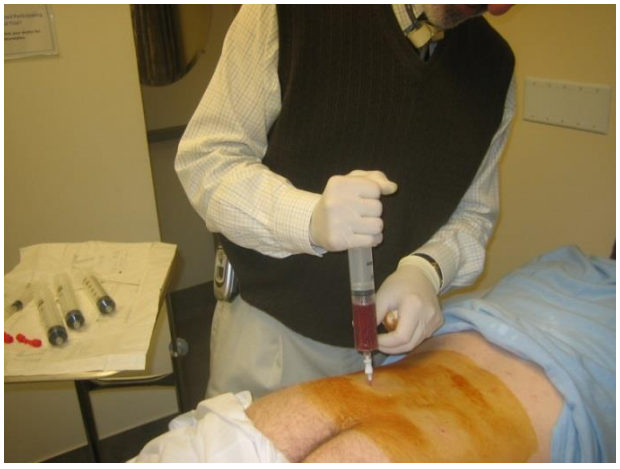
[Picture Credit: Blood Smear]

Patients with MDS often have too few red blood cells. They may have shortages of white blood cells and blood platelets as well. Patients with RAEB (refractory anaemia with excess blasts) may have a small number of myeloblasts in the blood.

Blood abnormalities may suggest MDS, but the doctor cannot make an exact diagnosis without examining a sample of bone marrow cells.

Other blood tests - the doctor may also order tests to check for other possible causes of low blood counts, such as low levels of Vitamin B_{12} and folate.

Bone marrow tests - bone marrow samples are obtained from a bone marrow aspiration and biopsy, tests that are usually done at the same time. The samples are usually taken from the back of the pelvic (hip) bone.



[Picture Credit: Bone Marrow Aspiration]

For a bone marrow *aspiration*, the patient lies on a table (either on his/her side or on the belly). After cleaning the area, the skin over the

hip and the surface of the bone is numbed with local anaesthetic, which may cause a brief stinging or burning sensation. A thin, hollow needle is then inserted into the bone and a syringe is used to suck out a small amount of liquid bone marrow (about 5ml). Even with the anaesthetic, most patients still have some brief pain when the marrow is removed.

A bone marrow *biopsy* is usually done just after the aspiration. A small piece of bone and marrow is removed with a needle that is twisted as it is pushed down into the bone. The biopsy may also cause some brief pain. Once the biopsy is done, pressure will be applied to the site to help prevent bleeding.

A pathologist (a doctor specialising in the diagnosis of diseases using laboratory tests) examines the bone marrow samples under a microscope. A haematologist (a doctor specialising in medical treatment of diseases of the blood and blood-forming tissues) or an oncologist (a doctor specialising in medical treatment of cancer) usually reviews these as well.

The doctors will look at the size and shape of the cells and see whether the red cells contain iron particles or whether the other cells contain granules (microscopic packets of enzymes and other chemicals that help white blood cells fight infections). The percentage of marrow cells that are blasts is particularly important. Blasts are very early cells that are produced by bone marrow stem cells. Blasts eventually mature into normal blood cells. In MDS, the blasts do not mature properly, so there may be too many blasts and not enough mature cells. For a diagnosis of MDS, a patient must have less than 20% blasts in the bone marrow. A patient who has more than 20% blasts in the bone marrow is considered to have acute leukaemia.

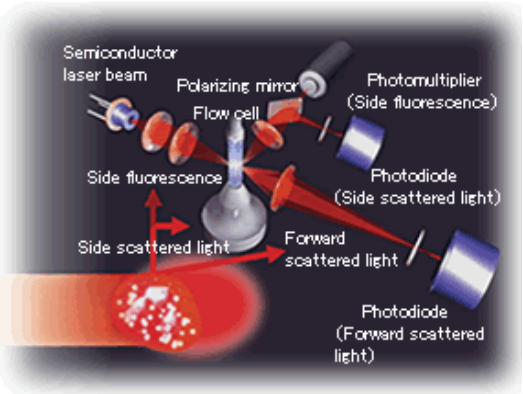
[Picture Credit: Microscopy]

Different types of tests that may be done on the bone marrow help the doctor diagnose MDS:

Immunocytochemistry - cells from the bone marrow sample are treated with special antibodies that cause certain types of cells change colour. The colour change can be seen only under a microscope. This testing is helpful in distinguishing different types of MDS or leukaemia from one another and from other diseases.

[Picture Credit: Flow Cytometry]

Flow cytometry - this technique is sometimes used to examine the cells from bone marrow and blood samples. It is very helpful in diagnosing and classifying the type of MDS. It is also used in diagnosing leukaemia and lymphoma. A sample of cells is treated with special antibodies and passed in front of a laser beam. Each antibody sticks only to certain types of cells. If the sample contains those cells, the laser will cause them to give off light. The instrument detects the light, and a computer counts the cells. This test may not be needed for all



patients.

Cytogenetics - this test looks at the chromosomes inside the cells. DNA in human cells is packed into chromosomes. Each cell should have 46 chromosomes (23 pairs). Abnormal chromosomes are common in MDS. Sometimes parts of chromosomes or even whole chromosomes are missing. MDS cells may also have extra copies of all or part of some chromosomes. Chromosome translocations (portions of chromosomes may trade places with each other) may also be seen.

Cytogenetic testing can take several weeks because the bone marrow cells need time to grow in laboratory dishes before their chromosomes can be viewed under the microscope.

Molecular genetic studies - these tests are another way to find chromosome and gene abnormalities. An example of this is *fluorescent in situ hybridization* – more commonly called FISH. In FISH, specific gene sequences are tagged with a fluorescent dye. These may correspond to a certain area of a chromosome or even a certain translocation. An advantage of FISH is that it doesn't require actively dividing cells. This allows the testing to go a bit faster than cytogenetic testing. FISH is very good for finding translocations – it can even find some that may be too small to be seen with usual cytogenetic testing.

[Picture Credit: Molecular Genetics]

Polymerase chain reaction (PCR) is another molecular genetic test that may be used to look for specific gene abnormalities.

Haase, D., Stevenson, K.E., Neuberg, D., Maciejewski, J.P., Nazha, A., Sekeres, M.A., Ebert, B.L., Garcia-Manero, G., Haferlach, C., Haferlach, T., Kern, W., Ogawa, S., Nagata, Y., Yoshida, K., Graubert, T.A., Walter, M.J., List, A.F., Komrokji, R.S., Padron, E., Sallman, D., Papaemmanuil, E., Campbell, P.J., Savona, M.R., Seegmiller, A., Adès, L., Fenaux, P., Shih, L.Y., Bowen, D., Groves, M.J., Tauro, S., Fontenay, M., Kosmider, O., Bar-Natan, M., Steensma, D., Stone, R., Heuser, M., Thol, F., Cazzola, M., Malcovati, L., Karsan, A., Ganster, C., Hellström-Lindberg, E., Boultwood, J., Pellagatti, A., Santini, V., Quek, L., Vyas, P., Tüchler, H., Greenberg, P.L., Bejar, R. & International Working Group for MDS Molecular Prognostic Committee. 2019.
"Risk stratification is critical in the care of patients with myelodysplastic syndromes (MDS). Approximately 10% have a complex karyotype (CK), defined as more than two cytogenetic abnormalities, which is a highly adverse prognostic marker. However, CK-MDS can carry a wide range of chromosomal abnormalities and somatic mutations. To refine risk stratification of CK-MDS patients, we examined data from 359 CK-MDS patients shared by the International Working Group for MDS. Mutations were underrepresented with the exception of TP53 mutations, identified in 55% of patients. TP53 mutated patients had even fewer co-mutated genes but were enriched for the del(5q) chromosomal abnormality ($p < 0.005$), monosomal karyotype ($p < 0.001$), and high complexity, defined as more than 4 cytogenetic abnormalities ($p < 0.001$). Monosomal karyotype,

high complexity, and TP53 mutation were individually associated with shorter overall survival, but monosomal status was not significant in a multivariable model. Multivariable survival modeling identified severe anemia (hemoglobin < 8.0 g/dL), NRAS mutation, SF3B1 mutation, TP53 mutation, elevated blast percentage (>10%), abnormal 3q, abnormal 9, and monosomy 7 as having the greatest survival risk. The poor risk associated with CK-MDS is driven by its association with prognostically adverse TP53 mutations and can be refined by considering clinical and karyotype features."

Complications of Myelodysplastic Syndrome (MDS)

Complications may include:

- Anaemia. Reduced numbers of red blood cells can cause anaemia, which can make one feel tired
- Recurrent infections. Having too few white blood cells increases the risk of serious infections
- Bleeding that will not stop. Lacking platelets in the blood to stop bleeding can lead to excessive bleeding that will not stop
- Increased risk of cancer. Some people with myelodysplastic syndromes may eventually develop leukaemia, a cancer of the blood cells

Treatment of Myelodysplastic Syndrome (MDS)

The main types of treatment for MDS may include:

- Supportive therapy
- Administration of growth factors
- Chemotherapy
- Immunotherapy
- Total body irradiation before stem cell transplant
- Stem cell transplant
- A combination of some of the above

Fennaux, P., Platzbecker, U. & Ades, L. 2020.

"The prognosis in Myelodysplastic syndromes (MDS), although recently refined by molecular studies, remains largely based on conventional prognostic scores [International Prognostic Scoring System (IPSS), revised IPSS], classifying patients into "lower risk" MDS (LR-MDS) and "higher risk" MDS (HR-MDS). In LR-MDS, treatment mainly aims at improving cytopenias, principally anaemia, while in HR-MDS it aims at delaying disease progression and prolonging survival. In LR-MDS without deletion 5q, anaemia is generally treated first by erythropoietic stimulating factors, while second line treatments are currently not approved [lenalidomide, hypomethylating agents (HMA), luspatercept] or rarely indicated (antithymocyte globulin). Lenalidomide has major efficacy in LR-MDS with deletion 5q. Allogeneic stem cell transplantation (allo-SCT) is sometimes considered in LR-MDS, and iron chelation can be considered when multiple red blood cell transfusions are required. Allo-SCT is the only potentially curative treatment for HR-MDS; however, it is rarely applicable. It is generally preceded by intensive chemotherapy (IC) or HMA in patients with excess of marrow blasts (especially if >10%). In other patients, HMA can improve survival. The role of new drugs, including venetoclax or, in case of specific mutations, IDH1 or IDH2 inhibitors, is investigated. IC is mainly indicated as a bridge to allo-SCT, in the absence of unfavourable karyotype."

Garcia, J.S. 2020.
"BCL-2 is an antiapoptotic protein that plays a critical role acute and chronic leukemias. Venetoclax is an orally selective BCL-2 inhibitor and BH3 mimetic approved in chronic lymphocytic leukemia and in combination with low dose cytarabine or hypomethylating agent in acute myeloid leukemia for the treatment of patients unfit for intensive chemotherapy. This article reviews the biology of BCL-2, focusing on its relationship to the myeloid microenvironment, and discusses the rationale for BCL-2 inhibition in myelodysplastic syndrome (MDS). Clinical trials testing venetoclax in MDS patients are under way. Potential biomarkers for clinical response to BCL-2 inhibition are discussed. Therapeutic opportunities for venetoclax in the therapeutic landscape of MDS are explored."

Chandhok, N.S., Boddu, P.C., Gore, S.D. & Prebet, T. 2019.
Among the promising agents with preclinical and early phase efficacy in higher risk MDS, apoptosis targeting with BCL-2 inhibitors have been a standout. There is also a keen interest in immunotherapy, and targeted agents (genetic, signaling pathways, bispecific antibodies, antibody-drug conjugates, and others described in this review).

Monaco, F., Scott, B.L., Chauncey, T.R., Petersen, F.B., Storer, B.E., Baron, F., Flowers, M.E., Deeg, H.J., Maloney, D.G., Storb, R. & Sandmaier, B.M. 2019.
"A nonmyeloablative regimen of fludarabine and 200 cGy total body irradiation combined with post-grafting immunosuppression with mycophenolate mofetil and a calcineurin inhibitor facilitates allogeneic hematopoietic cell transplantation from HLA-matched related or unrelated donors in older patients and/or those with comorbidities. However, outcomes of prior studies have been disappointing in patients with myelodysplastic syndromes or myeloproliferative neoplasms due to high incidences of progression or graft failure (together termed hematopoietic cell transplantation-failure). We hypothesized that escalating the total body irradiation dose may improve the outcomes and subsequently performed a phase II total body irradiation dose-escalation trial. Patients with median age 66 years were enrolled in two arms to receive nonmyeloablative conditioning followed by hematopoietic cell transplantation with total body irradiation dose escalation for excessive hematopoietic cell transplantation-failure: Arm A: myeloproliferative neoplasm/myelodys-plastic syndrome low-risk (n=36) and Arm B: myelodysplastic syndrome high-risk/chronic myelomonocytic leukemia (n=41). Total body irradiation dose levels were: Level-1 (300 cGy), Level-2 (400 cGy), or Level-3 (450 cGy). Patients received intravenous fludarabine 30 mg/m2 x3 days. Total body irradiation was administered on day 0 followed by infusion of peripheral blood stem cells from HLA-matched related (n=30) or unrelated (n=47) donors. Post-grafting immunosuppression with mycophenolate mofetil and cyclosporine was administered. The primary endpoint was day 200 hematopoietic cell transplant failure, with the objective of reducing the incidence to <20%. Primary endpoint was reached on Arm A at dose Level-1 (300 cGy total body irradiation) with a cumulative incidence of day 200 hematopoietic cell transplant failure of 11%, and on Arm B at dose Level-3 (450 cGy) with a cumulative incidence of day 200 hematopoietic cell transplant failure of 9%. Increasing the total body irradiation dose leads to a higher success rate with nonmyeloablative conditioning by reducing relapse and rejection. Further studies are necessary to decrease nonrelapse mortality, especially among patients with high-risk disease."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Medical Disclaimer

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Smoking
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