Introduction
The term ‘lymphoma’ refers to cancers that originate in the body's lymphatic tissues. Lymphatic tissues include the lymph nodes (also called lymph glands), thymus, spleen, tonsils, adenoids, and bone marrow, as well as the channels (called lymphatics or lymph vessels) that connect them. Although many types of cancer eventually spread to parts of the lymphatic system, lymphomas are distinct because they actually originate there.

![Lymphatic System of a Child](Image)

It is said that about 150 children younger than 19 years old are diagnosed with lymphoma each year in South Africa. Lymphomas are divided into three broad categories, depending on the appearance of their cancerous (malignant) cells. These are known as Hodgkin's lymphoma (HL), non-Hodgkin lymphoma (NHL), and Burkitt Lymphoma (BL). Together, they are one of the most common types of cancer in children.

Part of the body's immune system, the lymphatic system is a network of vessels and nodes that normally filters the fluid found within all tissues. Lymph nodes remove bacteria and other disease-causing organisms from the lymph fluid, and produce lymphocytes and antibodies needed to fight off infections caused by these organisms. An increase in the size of a lymph node (lymphadenopathy) indicates increased activity within the node, due to inflammation, infection, or cancer.

Malignancy (cancer) occurs when a cell's genetic code mutates, or changes, resulting in abnormal cells that grow rapidly and in uncontrolled fashion. Lymphomas are a group of
cancers originating from lymphocytes, which are white blood cells whose normal function is
to fight off infections within the body. (KidsHealth; LymphomaInfo.Net).

**Incidence of Lymphoma in Children**
The incidence of the different types of lymphoma is provided under the description of each of
the lymphomas.

**Symptoms of Lymphoma in Children**
Warning signs for lymphoma are similar in children and adolescents as well as in adults.
Symptoms include:

- One or more enlarged lymph nodes in the neck, underarm, or groin, which are
  usually painless
- Chills
- Swelling of the lymph nodes, which may or may not be painless
- Abdominal swelling (lymphomas in the chest or abdomen can grow to a very large
  size before symptoms appear)
- Unexplained fever
- Night sweats
- Loss of appetite
- Unexplained weight loss
- Lack of energy
- Coughing
- Difficulty in breathing
  - Itchiness

If a child has a lymph node that becomes enlarged without explanation or remains enlarged
for a prolonged period of time, a paediatrician should be consulted. He/she may prescribe a
course of antibiotics to treat a possible infection before performing a more extensive
evaluation (Memorial Sloan Kettering Cancer Center; Lymphoma Research Foundation).

**Causes and Risk Factors of Lymphoma in Children**
Although the causes of lymphoma remain unknown, the following may increase the risk of
childhood or adolescent lymphomas:

- Family history (though no hereditary pattern has been firmly established)
- Presence or history of an autoimmune disease
- Receipt of an organ transplant
- Exposure to chemicals such as pesticides, fertilizers or solvents
- Infection with viruses such as Epstein-Barr, human T-lymphotropic virus type 1, HIV,
  hepatitis C, or certain bacteria such as *Helicobacter pylori*

The cause of lymphoma is not known, but there is a genetic component. Incidence rates are
higher for those who have a family member diagnosed with lymphoma, especially a sibling.
While environmental and lifestyle factors are known to play a role in the development of
cancer among adults, these factors have less of an impact on the development of childhood cancer.  
(Lymphoma Research Foundation; LymphomaInfo.Net).

**Hodgkin’s Lymphoma**

Cancer cells of these patients are usually abnormal B-cells referred to as a Reed-Sternberg (R-S) cells. Although less commonly observed, R-S cells may also develop from T-cells. R-S cells most often develop in lymph nodes located in the upper body regions and spread to neighbouring lymph nodes via lymphatic vessels. There are two distinct types of Hodgkin's lymphoma: classical and non-classical Hodgkin's lymphoma.

- Classical Hodgkin's Lymphoma: This lymphoma features R-S cells with a classical appearance. It may be diagnosed as Nodular Sclerosis Hodgkin Disease, Mixed Cellularity Hodgkin’s Disease, Lymphocyte-Rich Hodgkin Disease or Lymphocyte-Depleted Hodgkin Disease.
- Non-classical Hodgkin’s Lymphoma: This lymphoma features larger cancer cells that are variants of R-S cells and is most often found in the nodes of the upper body, arms and neck.

Classical Hodgkin lymphoma is divided into four subtypes, based on how the cancer cells look under a microscope:
- Lymphocyte-rich classical Hodgkin lymphoma.
- Nodular sclerosis Hodgkin lymphoma.
- Mixed cellularity Hodgkin lymphoma.
- Lymphocyte-depleted Hodgkin lymphoma.  
(National Cancer Institute).

**Incidence of Childhood Hodgkin’s Lymphoma**

According to the National Cancer Registry (2012) the following number of Hodgkin’s Lymphoma cases were histologically diagnosed in South Africa during 2012:

<table>
<thead>
<tr>
<th>Group</th>
<th>Actual No of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>All boys 2012</td>
<td>46</td>
</tr>
<tr>
<td>Asian boys</td>
<td>0</td>
</tr>
<tr>
<td>Black boys</td>
<td>37</td>
</tr>
<tr>
<td>Coloured boys</td>
<td>4</td>
</tr>
<tr>
<td>White boys</td>
<td>5</td>
</tr>
</tbody>
</table>
The frequency of histologically diagnosed cases of Hodgkin Lymphoma in South Africa for 2012 was as follows (National Cancer Registry, 2012):

<table>
<thead>
<tr>
<th>Group</th>
<th>Actual No of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls: 0 to 19 Years 2012</td>
<td></td>
</tr>
<tr>
<td>All girls</td>
<td>26</td>
</tr>
<tr>
<td>Asian girls</td>
<td>0</td>
</tr>
<tr>
<td>Black girls</td>
<td>16</td>
</tr>
<tr>
<td>Coloured girls</td>
<td>4</td>
</tr>
<tr>
<td>White girls</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>0 – 4 Years</th>
<th>5 – 9 Years</th>
<th>10 – 14 Years</th>
<th>15 – 19 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys: 0 to 19 Years 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All boys</td>
<td>1</td>
<td>17</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Asian boys</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Black boys</td>
<td>1</td>
<td>14</td>
<td>12</td>
<td>10</td>
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<tr>
<td>Coloured boys</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>White boys</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>0 – 4 Years</th>
<th>5 – 9 Years</th>
<th>10 – 14 Years</th>
<th>15 – 19 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls: 0 to 19 Years 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All girls</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Asian girls</td>
<td>0</td>
<td>0</td>
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<td>Black girls</td>
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<tr>
<td>Coloured girls</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>White girls</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

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 boys’ and ‘all girls’, however, always reflect the correct totals.

Diagnosis of Hodgkin’s Lymphoma (HL)

The following tests and procedures may be used:

Physical examination and history - an examination of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments will also be taken.

CT Scan (CAT scan) - a procedure that makes a series of detailed pictures of areas inside the body, such as the neck, chest, abdomen, or pelvis, taken from different angles. The pictures are made by a computer linked to an X-ray machine A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. This procedure is also called computed tomography, computerized tomography, or computerized axial tomography. Pet Scan (positron emission tomography scan) – a procedure to find malignant tumour cells in the body. A small amount of radioactive glucose (sugar) is injected into a vein. The PET scanner rotates around the body and makes a picture of where glucose is being used in the body. Malignant tumour cells show up brighter in the picture because they are more active and take up more glucose than normal cells do. Sometimes a PET scan and a CT scan are done at the same time. If there is any cancer, this increases the chance that it will be found.

Chest X-ray - an X-ray of the organs and bones inside the chest. An X-ray is a type of energy beam that can go through the body and onto film, making a picture of areas inside the body.
Complete Blood Count (CBC) - a procedure in which a sample of blood is drawn and checked for the following:

- The number of red blood cells, white blood cells, and platelets.
- The amount of haemoglobin (the protein that carries oxygen) in the red blood cells.
- The portion of the blood sample made up of red blood cells.

Blood Chemistry Studies - a procedure in which a blood sample is checked to measure the amounts of certain substances released into the blood by organs and tissues in the body. An unusual (higher or lower than normal) amount of a substance can be a sign of disease in the organ or tissue that makes it.

Sedimentation Rate - a procedure in which a sample of blood is drawn and checked for the rate at which the red blood cells settle to the bottom of the test tube.

Lymph node biopsy - the removal of all or part of a lymph node. The lymph node may be removed during a thoracoscopy, mediastinoscopy, or laparoscopy. One of the following types of biopsies may be done:

- Excisional biopsy - the removal of an entire lymph node.
- Incisional biopsy - the removal of part of a lymph node.
- Core biopsy - the removal of tissue from a lymph node using a wide needle.
- Fine-needle aspiration (FNA) biopsy - the removal of tissue from a lymph node using a thin needle.

A pathologist views the tissue under a microscope to look for cancer cells, especially Reed-Sternberg cells. Reed-Sternberg cells are common in classical Hodgkin lymphoma.

The following test may be done on tissue that was removed:

- Immunophenotyping - a laboratory test used to identify cells, based on the types of antigens or markers on the surface of the cell. This test is used to diagnose the specific type of lymphoma by comparing the cancer cells to normal cells of the immune system.

(Total Cancer Institute).

Treatment of Childhood Lymphoma
Treatment of childhood lymphoma is largely determined by staging. Staging is a way to categorise or classify patients according to how extensive the disease is at the time of diagnosis.

Chemotherapy (the use of highly potent medical drugs to kill cancer cells) is the primary form of treatment for all types of lymphoma.

In certain cases, radiation therapy (the use of high-energy rays to shrink tumours and keep cancer cells from growing), may also be used.

Short-term and long-term side effects - Intensive lymphoma chemotherapy affects the bone marrow, causing anaemia and bleeding problems, and increasing the risk for serious infections. Chemotherapy and radiation treatments have many other side effects — some short-term (such as hair loss, changes in skin colour, increased infection risk, and nausea
and vomiting) and some long-term (such heart and kidney damage, reproductive problems, thyroid problems, or the development of another cancer later in life) — that parents should discuss with their doctor.

Relapses - Although most kids do recover from lymphoma, some with severe disease will have a relapse (reoccurrence of the cancer). For these children, bone marrow transplants and stem-cell transplants are often among the newest treatment options.

During a bone marrow/stem cell transplant, intensive chemotherapy with or without radiation therapy is given to kill residual cancerous cells. Then, healthy bone marrow/stem cells are introduced into the body in the hopes that it will begin producing white blood cells that will help the child fight infections.

New Treatments - Promising new treatments being developed for childhood lymphomas include several different types of immunotherapy, specifically the use of antibodies to deliver chemotherapy medicines or radioactive chemicals directly to lymphoma cells. This direct targeting of lymphoma cells may avoid the toxic side effects that occur when today's chemotherapy and radiation treatments damage normal, noncancerous body tissues. (Kids Health).

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.

(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 condition or situation. Readers of this document should seek appropriate medical advice prior to taking or refraining from taking any action resulting from the contents of this Fact Sheet. As far as permissible by South African law, the Cancer Association of South Africa (CASNA) accepts no responsibility or liability to any person (or his/her dependants/estate/heirs) as a result of using any information contained in this Fact Sheet.

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http://www.cancer.gov/cancertopics/pdq/treatment/childhood&gclid=CMT7_K6E5b4CFUXnwgodKBCapw

Non-Hodgkin’s Lymphoma

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May 2017