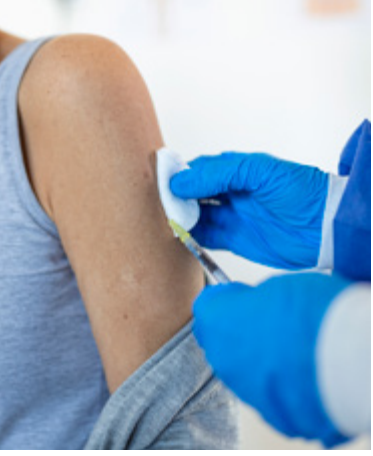
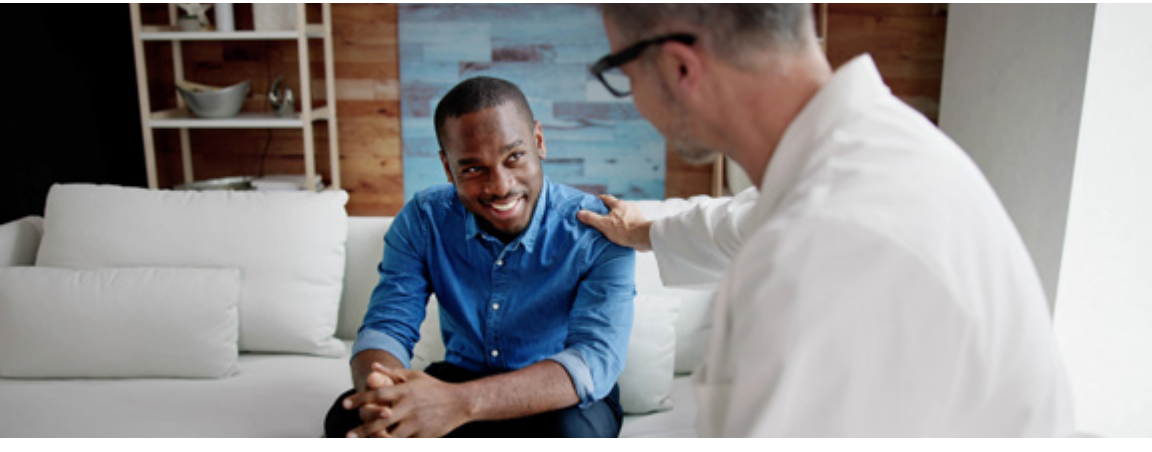


Myeloma Canada
InfoGuide Series

Clinical Trials: Are they an Option for me?



MYELOMA CANADA

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Myeloma Canada wishes to acknowledge and thank the Myeloma Canada's Patient Advisory Council (PAC), the Quebec – Clinical Research Organization in Cancer (Q-CROC) and the many individuals in our community who provided their invaluable input.

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Introduction

Over the past 30 years, research has increased our understanding of myeloma and its underlying disease processes. This has led to the development and approval of new treatments with novel drugs that have extended the lives of people living with myeloma.

This InfoGuide is written for patients with myeloma, their families and friends. It is intended to help clarify and explain the clinical trial process and answer frequently asked questions. The information provided can help with decision-making on whether a clinical trial is the right option for a patient.

Clinical trials are research studies done with patients to evaluate new treatments or new ways of combining and administering existing treatments. By testing new drugs or combinations of drugs, each study's ultimate goal is to find better ways to treat the disease, as well as improve quality of life. This is done by answering precise scientific questions asked in each study protocol.

This InfoGuide aims to:

- Help you understand more about clinical trials and how they work
- Help you understand what is involved in a clinical trial, their advantages and disadvantages
- Provide information to caregivers and family members

Some of the more technical or unusual words appear in ***bold italic*** the first time they are used and are explained in the **Glossary** on **page 27**. Don't be afraid to ask members of your healthcare team to explain any terms or concepts you may have trouble understanding.

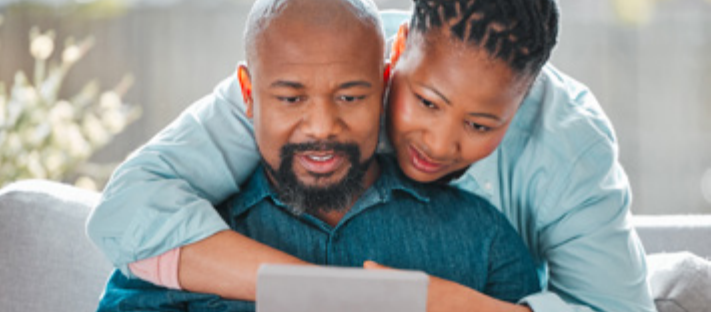
Throughout your journey with myeloma, your healthcare team will provide you with a large amount of information about your potential treatment options, the disease itself, and more. Early identification, assessment and the treatment of symptoms is key. You may find it helpful to write down any questions you have along the way and share these with your healthcare team regularly. They are the best people to help you understand what is happening and guide you to make informed decisions.

Be an informed and cautious information consumer

Be cautious of information that comes your way. While books and the internet offer a wealth of information, not all of it is correct, it may not apply to your unique situation, and it may be confusing or misleading. Well-intended people may also try to offer you health advice without knowing the details of your condition and its treatment. Certain online support groups may also be helpful, but again be wary of possible misinformation. It's important to know that your source is reputable and to discuss what you read with your healthcare team. Never make any change to your treatment plan without checking with them first, and discuss any symptom you're experiencing.

To ensure you have the most reliable, up-to-date information and resources, visit the Myeloma Canada website, myeloma.ca often. There you will also find helpful links to support groups and programs, educational events and videos, and more.

Table of contents



What is multiple myeloma?

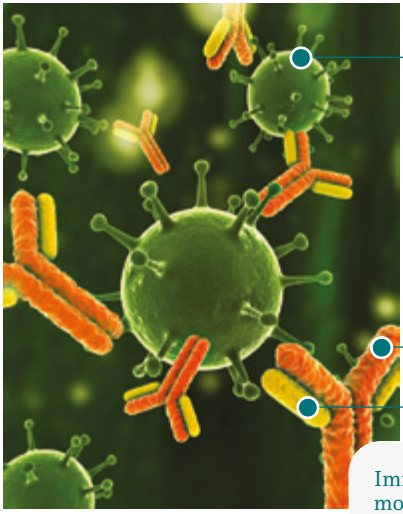
Multiple Myeloma is a cancer of the ***plasma cells***. The word "multiple" is often used because myeloma cells usually affect multiple areas of the ***bone marrow***. In this resource, we'll use the term "myeloma" to keep things simple. While a cure for myeloma has yet to be developed, scientific breakthroughs have made it a treatable disease and people with myeloma are living longer and with better quality of life. In fact, for many people myeloma is becoming a chronic disease.

Myeloma and its pre-cursors, monoclonal gammopathy of undetermined significant (MGUS) and smouldering multiple myeloma (SMM), are a group of conditions and diseases that fall under the category of plasma cell disorders. In a nutshell, a plasma cell is a type of white blood cell (WBC) produced in the bone marrow, the "blood factory" located within the hollow area of bones, that produces ***antibodies (immunoglobulins)*** to fight infection (refer to Figure 1). Myeloma is the 2nd most common form of hematologic (blood) cancer and may also be referred to as a cancer of the immune cells.

Abnormal accumulation of myeloma cells in your bone marrow have direct and indirect effects on your blood, bone and kidneys. Myeloma's signs and symptoms are often vague and thus are attributed to aging or other more common causes or conditions. Myeloma can present itself in many different ways:

- Elevated blood calcium (hypercalcemia)
- Kidney (renal) damage
- Low hemoglobin (anemia)
- Persistent bone pain and/or fractures (lesions)
- Frequent or recurring infections
- Fatigue, weakness, shortness of breath

Figure 1: Structure of an antibody (immunoglobulin)



Immunoglobulins (antibodies) are Y-shaped molecules. The heavy and light chains of the antibody contain specific binding sites that attach to bacteria or viruses, ultimately leading to their destruction thereby protecting against disease.

Diagnosis of myeloma requires an evaluation and work up by a hematologist/oncologist.

For more information on plasma cell disorders, please consult Myeloma Canada's Multiple Myeloma Patient Handbook as well as the MGUS and Smouldering Multiple Myeloma InfoGuide.

Clinical trials: A treatment option for myeloma

Overview

Based on the specifics of your myeloma diagnosis, a participation in a ***clinical trial*** may be an option to consider. There are clinical trials that are designed for each phase of the disease: from ***smouldering myeloma*** to newly-diagnosed to relapsed and refractory disease. Except for post-marketing studies (defined as phase IV studies, refer to page 10) the drugs or combinations of treatments being studied in clinical trials are usually not yet approved by Health Canada, because their safety and efficacy have not yet been fully evaluated.

More information

The drug development process & pre-clinical testing

Typically, the process of developing a new drug takes many years and hundreds of millions of dollars. After a drug has been manufactured, it is purified (isolated) in the research laboratory and tested in pre-clinical studies with human cells on a petri dish or in a test tube *(in vitro)* and with laboratory animals *(in vivo)*. These small studies aim at gathering as much information as possible on the drug's dosage, efficacy, safety and toxicity.

After pre-clinical testing, the researchers review their findings and decide whether the drug should be tested in humans. The study results are then sent to the Health Products and Food Branch (HPFB) of Health Canada as part of an application for authorization to conduct a clinical trial to study the drug in Canadian patients.

Key terminology

Standard of care
A routine approach (medicine or procedure) recommended to patients who have a certain disease and who share the same or similar circumstances. Standard of care is accepted by medical experts as being an appropriate clinical approach that is widely

applied by a prudent and qualified healthcare professional. For certain conditions, the standard of care may be no treatment or observation (as in smouldering myeloma). Standard of care can also be referred to as best practice, standard medical care or standard therapy.

Placebo

A harmless and inactive pill (sometimes referred to as a "sugar pill") or injection indistinguishable from the drug being tested. The placebo is used in some clinical trials to control for the "placebo effect," a positive psychological effect generally associated with treatment. It would be unethical to provide no treatment or only a placebo in a study on a serious disease like cancer, if a treatment is actually available. For example, in such a case, participants could be given the standard of care treatment, with the study drug or with a placebo.

Arms

Treatment groups in clinical trials, example:

- **Experimental arm:** Receives the standard of care with the treatment being studied*
- **Control arm:** Receives the standard of care with a placebo

* **Note:** If the standard of care is observation only, all participants would receive the study drug, without randomization, nor any placebo.

Randomized controlled trial

In trials with more than one arm, participants are randomly assigned to a group (arm or cohort) receiving a particular treatment, either the treatment being studied (experimental arm/cohort) or the standard of care (control arm/cohort).

Control arm cross-over

Cross-over may be possible for participants in the control arm. For instance, if a participant receiving the standard of care treatment is no longer responding to the treatment, some trials allow the patient to "cross-over" to the experimental arm and receive the treatment being studied. **Note:** Not all studies allow for cross-over; this will be communicated to you at the beginning of the study, or you can ask your doctor or nurse before you sign the informed consent form (see page 12).

Open label and blinded (or "masked") studies

In *open label studies,* both the research team and the participants are aware of the drug or treatment the participants are receiving.

In contrast, participants in *single-blinded studies* do not know which treatment(s) they are receiving. In *double-blinded studies,* both the participants and all members of the research team do not know which treatment(s) the participants are receiving.

Blinded studies are designed to prevent members of the research team or study participants from unintentionally influencing the results. They are designed to produce data that are not influenced by bias or expectations from the participants or researchers, thus allowing for scientifically accurate conclusions of the actual benefits and ***side effects (adverse events)*** of the treatment being studied.

For example:
In *blinded* studies with two arms, a prespecified portion of the participants receive the treatment being studied (experimental arm), while the other portion receives the standard of care treatment alone or with placebo (control arm).

In open label studies with two arms, a prespecified portion of the participants receive the treatment being studied (experimental arm), while the other portion receives the standard of care treatment without placebo (control arm).

Type of Study	Experimental Arm	Control Arm
Open label	Treatment being studied	Standard of care treatment
Blinded	Treatment being studied	Standard of care treatment + Placebo

Common myths about clinical trials

MYTH: You will receive placebo only and not receive treatment

In clinical trials for myeloma, it is unethical to receive no treatment or a placebo on its own, unless the standard of care is no treatment or observation. For example, in past studies that looked at post-transplant ***maintenance therapy***, the control arm was no treatment because the post-transplant standard of care was observation only at the time the trials were being conducted. "Placebo only" groups are also used in studies that look at how cancer is prevented.

MYTH: Clinical trials are only appropriate as the "last option"

Experimental treatments may be available to be tested at any stage of a disease.

MYTH: No access to the treatment being studied when the clinical trial is over

After the completion of a clinical trial, if the participant is still on the experimental treatment and responding, they may be offered to continue receiving this treatment on an "extension arm". In the event that the study drug is not commercially available and there is no extension arm, physicians and research coordinators may be able to arrange for the drug to be used under ***compassionate access.***

More information

Quality of life assessment questionnaires

Improving the quality of life of patients is a very important goal of clinical trials that compare treatments. Study protocols will often include quality of life assessment questionnaires and healthcare economic questionnaires, or they may be part of a separate quality of life sub-study. These surveys usually ask patients to rate, on a scale, their perceptions of their emotional, social, physical and cognitive symptoms, as well as treatment side effects and managing life at home and at work. Healthcare economic questionnaires ask questions about how often patients or their caregivers are unable to work because of appointments, side effects or treatments, and number of hospitalizations while on the study. This is to find out whether the study treatment negatively impacted the patient and/or their family financially, as well as the healthcare system. Study participants may also be asked to keep a detailed diary of how they feel after treatment, including side effects and the frequency of use of supportive medications (e.g., painkillers).

Thus, tracking patient's quality of life is crucial to establishing treatments with fewer side effects, less hospital visits and less financial burden. Furthermore, the information collected can also be submitted for ***health technology assessment*** and favourably impact provincial drug reimbursement decisions.

MYTH: Clinical trials are not safe

Volunteers who participate in clinical trials are fully informed about the possible risks and benefits of the study. They are tested and assessed frequently to monitor their safety. Specialized doctors, nurses, and other research staff will closely follow them throughout the trial, and possibly for a long period after the trial is finished to evaluate if there are any long-term effects (while taking the drug and beyond) or latent effects (months or years after stopping the drug) of the study treatment.

MYTH: Clinical trials are expensive for patients

Most clinical trials are not financially burdensome. Generally, clinical trials are at little or no expense to participants. Out of pocket expenses incurred during a clinical trial are sometimes reimbursed to participants.

More information

Travel considerations & grants

If you live far away from the centre that is conducting the clinical trial, you may be required to travel long distances for treatment and/or follow-up appointments. This may result in substantial logistical hurdles, or you may simply not be able to afford to travel to and from the treatment centre. Depending on the province you live in, you may be eligible for a travel grant. In fact, many pharmaceutical companies will also reimburse any out-of-pocket expenses like travel, parking, hotel and meals. Ask the clinical trial coordinator or the centre's supportive care counsellor about programs you may be eligible for.

About clinical trials

Overview

Clinical trials allow researchers to gather information on a drug's dose, effectiveness and safety in humans. Their ***study protocol (written plan)*** is designed to answer key research questions by comparing results from the different treatment arms (groups) that include either the experimental drug, standard of care, standard of care plus placebo or their various combinations. These studies can be conducted by a single researcher in one hospital or clinic, or by many researchers in one or many countries.

Because clinical research involves both drugs and people, there are strict regulations in place to ensure the safety of participants. For instance, Phase I, II and III (read more about the different phases of clinical trials on page 9) clinical trials are approved and supervised by:

- Health Canada
- Ethics committees or boards at each of the participating hospitals or clinics, and sometimes also by a Data Safety Monitoring Board (DSMB), an independent group of experts

These various regulatory bodies require the ***sponsor*** (pharmaceutical company and/or investigator) of the research to track, evaluate and report any issues concerning participant safety and quality of the data generated by the study. These checks are in place to demonstrate compliance of the sponsor/investigator with regulations and the standards of "Good Clinical Practice".

More information

Safety & monitoring

In clinical trials there are many unknowns, including short-term and long-term side effects of the drug being evaluated, and treatment efficacy. Numerous safeguards are in place to help minimize potential risks. Regulations and regulatory body oversight help maintain the balance between medical progress and patient safety. Additionally, the research team will work with your healthcare team to make sure that your participation in the study is safe.

It is possible that participants undergo more tests during a trial and have more doctor visits compared to the regular care setting. This would be explained to you during the informed consent discussion.

Clinical trial phases

There are four phases or types of clinical trials, and each one is designed to answer specific questions. The therapy being evaluated can involve a new drug, a new combination of drugs or a new dosing schedule.

Phase I - What is the best and safest way to administer the new therapy?
Phase I trials are designed to determine the optimal safe dose for a new drug that has either never been tried in humans or is a new combination of drugs. These trials involve a small number of myeloma patients. This phase can also assess the safety, tolerability, side effects, pharmacokinetics (how the body copes with and excretes the drug), pharmacodynamics (how the drug works in the body) and efficacy (how well it works) of a new drug. A range of ascending doses are often tested, and dosing starts at just a fraction of the dose that was shown to cause harm in animal testing. Dosing continues to ascend until a dose limiting toxicity (DLT) is found (a side effect that causes unacceptable toxicity in 1 or more participants). This is called the maximum tolerated dose (MTD).

Phase II - Does the new treatment work in a selected group of patients?
Phase II trials typically involve larger groups of participants compared to Phase I trials. The selected participants will reflect a particular type or stage of the myeloma being treated. Using the MTD established during Phase I testing, the goal of the trial is to evaluate how effective the new treatment is in treating that type or stage of the myeloma in the selected group of patients. All participants in this phase receive the same starting dose. If side effects occur, the dose can be decreased.

Phase III - Is the new treatment more effective than the standard of care?
Only therapies that were proven effective and safe, with tolerable side effects, can proceed to Phase III testing. Phase III trials compare the standard of care to the new treatment and usually involve hundreds or even thousands of people at cancer centres around the world.

Phase IV - Does the new agent work well in the "real world"?
Phase IV trials are sometimes referred to as "post marketing research" or "expanded access program or trial" and are carried out with a drug that has already been approved by Health Canada and may be used by doctors. These trials may be conducted for a variety of reasons such as testing for interactions with other drugs or evaluating the effectiveness of a drug in a more natural and less controlled setting, as well as collecting long term side effect data. The true safety profile of a drug can only be established by continuous safety surveillance that is designed to detect any rare or long-term side effects over a larger patient population and longer period of time than is possible during Phase I–III trials.

Summary of clinical trial phases

Phase	Description
I	• Usually 15 to 30 people • To find the safe MTD • To decide how the treatment should be given (e.g., orally, by injection [***subcutaneously***], or by infusion [***intravenously***])? • To observe how the treatment affects the human body
II	• Usually less than 100 people • Uses the MTD established during Phase I • To determine if the treatment has an effect on a particular stage of cancer • To see how the treatment affects the human body
III	• From 100 to 1,000 people • To compare a new agent or intervention (or new use of a treatment) with the current standard of care
IV	• Several hundred to several thousand people • To further evaluate the long-term safety and effectiveness of a new treatment in the "real world"

Safeguards that ensure the protection of study participants

To ensure participant safety and data quality, everyone involved in the study must play an active role.

Pharmaceutical company or sponsor of the study

The sponsor of the study must demonstrate the merits of the study to outside experts who will evaluate the proposed design and purpose of the study.

Principal investigator

The main role of the study's ***principal investigator (PI)*** is to prepare the study protocol/plan (for investigator-initiated studies; see page 16 for more information), supervise the study and ensure that all approvals (e.g., ethics, hospital, Health Canada) have been received prior to starting a trial. Many institutions/centres may offer the same clinical trial and the same protocol is used at each one.

Institutional Review Boards (IRBs)/Research Ethics Boards (REBs)

An IRB/REB is an independent, stand-alone entity not funded by or related to any investigator, manufacturer or ***contract research and site management organization***. Their members include healthcare professionals, lawyers, statisticians and lay people, and they are compensated on a consulting basis, irrespective of their review decisions. Board members do not have financial or other conflicts of interest concerning the clinical trial under evaluation. The IRB/REB's overarching mission is to protect human research participants and provide a thorough ethical and scientific review of the research project. They have power to approve, reject or request changes to be made before approving the study. As part of their mandate, they can decide how often to review the trial once it has begun and whether to stop it if:

- the protocol is not being followed by the investigator;
- the study intervention appears to be causing unexpected harm;
- a new intervention is shown to be potentially more effective than the study intervention.

Data Safety Monitoring Board (DSMB)

Trials are sometimes supervised by a DSMB, an independent committee made up of statisticians, physicians and other expert scientists that:

- periodically monitor trial data;
- ensure the data is complete.

If the treatment being studied seems to show an advantage for participants, the DSMB can recommend that the trial be ended early, so that the results can be immediately evaluated by regulatory agencies, for approval. A recommendation for a trial to be stopped early can also be made if there is evidence that the treatment being studied is not working or has severe and/or life-threatening side effects.

Eligibility (inclusion/exclusion) criteria

Certain requirements must be met in order to participate in a study. Both the ***inclusion criteria*** (conditions that participants must meet) and ***exclusion criteria*** (conditions that participants cannot have) are critical to get credible and consistent results. Here are examples of eligibility criteria: general well-being (performance status), age, type and stage of myeloma, laboratory test results, other illnesses or conditions and number and types of past treatments.

Informed consent process

The informed consent process aims at helping you make an educated decision about your participation in a clinical trial. It ensures that you have been provided with, and understand, all of the key facts about the clinical trial study protocol. This includes the treatments in each study arm, potential benefits and risks related to participating in the trial, financial considerations, confidentiality, and much more. The informed consent form summarises the important information about the trial.

Once you have read and understood the informed consent document, you will be asked to sign the document to confirm that you agree to participate. Beforehand, ensure to take enough time to have all your questions answered and to think about it. If you have any questions about the trial, you are encouraged to talk to your doctor or a member of the clinical trial team before and throughout the trial. You will receive a copy of your signed informed consent form including contact information for the study. You are encouraged to share this document with anyone you feel appropriate. Any time there are updates to the study, you will be informed with a revised consent form. You may also decide at any time to withdraw from the study.

More information

Dropout from study

Informed consent is voluntary. If you choose to not participate , your doctor or nurse will discuss your treatment options with you. If you have already enrolled in a study, you are free to withdraw from the study at any time, without providing a reason.

Participant withdrawal from study

Conditions for participant withdrawal are explained in the informed consent form and vary from study to study. If a participant is not compliant with the study requirements, they may be withdrawn from the study.

Know your rights as a research participant

As a research participant, you have the right to be treated fairly, respectfully, and be free from pressure and interference when making decisions. If you are requesting information

about a study, you also have the right to be told about:

- All of your options, apart from participation in the study
- What the trial is trying to find out
- The possible risks, side effects and benefits of the study
- What drugs, procedures or devices are different from what is used in standard care
- What treatments are available if any medical problems arise

Lastly, all personal information collected during a clinical trial is confidential and will be protected, even after you have completed or withdrawn from the study.

More information

Clinical trial results make a difference

We can gain insights and answer questions about the safety and effectiveness of new drugs or therapeutic approaches only through clinical research. Ground-breaking scientific advances in the past (and present) were made possible because of the participation of patients in clinical research. Their involvement is essential to help researchers better understand the disease and how to treat it more effectively.

Questions for your healthcare team

About the study

- What is the purpose of the study?
- Why do researchers think the approach may be effective?
- Who is funding the study?
- Who has reviewed and approved the study?
- How are the study results and safety of participants being checked?
- How long will the study last?
- What will be my responsibilities if I participate?
- Will my participation in the study restrict my treatment options in the future?

Possible risks and benefits

- What are the possible short- and long-term benefits and risks?
- What other options do I have?
- How do the possible risks and benefits of this trial compare to those other options?

Participation and care

- What kinds of therapies, procedures and/or tests will I have during the trial? Will they hurt, and if so, for how long?
- Will I be able to take my regular medications while in the clinical trial?
- How do the tests in the study compare to those I would have outside of the trial?
- Where will I have my medical care and who will be in charge of my care?

Personal issues

- How will my daily life be affected by participating in this study?
- Can I talk to other people who are participating in the study?

Cost issues

- Will I have to pay for any part of the trial such as tests or the study drug? If so, what will the charges likely be?
- Will there be any travel costs that I need to consider while I am in the trial?
- Will I be required to stay close to the treatment centre for a period of time in case there are delayed side effects?
- What will my health insurance likely cover?
- Who can help answer any questions from the insurance company?

Weighing the advantages & disadvantages

Participating in a clinical trial is completely voluntary. Before agreeing to participate, you must learn about the possible risks and benefits of a trial, what other options are available, extra responsibilities you may have etc. to determine if in your case, the advantages of participation outweigh the disadvantages. Potential participation should be discussed in depth with your healthcare team.

People participate in clinical trials for a variety of reasons, e.g. to help advance knowledge, because their cancer doesn't respond to available treatments, etc. Whether a person is newly diagnosed, has relapsed or has refractory disease, there is a number of possible advantages and disadvantages that come with participating in clinical trials.

Examples of possible advantages:

- Helping to better understand the disease
- Helping researchers find better treatments or advance myeloma research to improve the way patients will be treated in the future

Examples of possible disadvantages:

- Experiencing known and unknown side effects
- Extra time and costs related to traveling to the hospital or clinic for study visits
- Undergoing extra tests

Myeloma research in Canada

Canadian Myeloma Research Group (CMRG)

CMRG is the only organization dedicated solely to myeloma research in Canada. They are made up of over 50 researchers across 30 research centres and are recognized as a global leader in myeloma research. CMRG helps bring cutting edge laboratory discoveries into clinical trials quickly and efficiently for Canadian patients, has one of the largest and most comprehensive multiple myeloma databases in the world collecting real time patient data, and work with multiple centres across Canada to perform dynamic translational research. Learn more at www.cmrg.ca.

Canadian Cancer Trials Group (CCTG)

CCTG is an academic cooperative oncology group that designs and conducts clinical trials testing cancer therapy, supportive care and prevention interventions across Canada. The Group is a collaborative network of researchers, physicians, scientists, statisticians and patients internationally recognized for finding the treatments that give people with cancer longer, better quality lives. Learn more at www.ctg.queensu.ca.

(Quebec only) The Quebec – Clinical Research Organization in Cancer (Q-CROC)

Q-CROC is a non-profit organization that has been active since 2008. It coordinates a clinical cancer research network of 18 health care institutions across the province of Quebec and develops solutions to optimize participant recruitment and improve clinical research knowledge. Learn more at https://qcroc.ca/en.

(Quebec only) Oncopole

Oncopole, FRQS cancer division, is a hub for research, development and investment to accelerate the fight against cancer. The Oncopole's mission is to act as a catalyst leveraging actions made by the key players in Quebec's oncology and innovation research ecosystem. Its priorities of action, namely research, entrepreneurship, commercialization and integration of innovation, as well as clinical relevance, are orchestrated in order to foster the mobilization of stakeholders, the discovery of innovative approaches to fight cancer and, ultimately, a positive impact for the benefit of patients. Learn more at https://oncopole.ca/en.

More information

Find clinical trials in Canada

To search for clinical trials that are recruiting patients in Canada, please visit the following websites:

1. www.myeloma.ca/findtrials
   Find myeloma trials that are recruiting in Canada by disease stage and postal code.
2. www.cmrg.ca/research/clinical-trials
   The only organization dedicated solely to myeloma research in Canada
3. www.canadiancancertrials.ca
   A Canadian website that allows you to search by cancer type and location.
4. www.clinicaltrials.gov
   This website is a service provided by the U.S. National Institute of Health.
5. https://health-products.camada.ca/ctdb-bdec/index-eng.jsp
   Health Canada's Clinical Trials Database
6. (Quebec only) https://www.oncoquebec.com/home/onco-plus
   Onco+ is a free support service that helps guide any cancer patient, caregiver or health care professional looking for a clinical trial.

More information

Industry-initiated and investigator-initiated trials

Pharmaceutical companies can either sponsor their own clinical trials or support investigator-initiated (academic) trials. In both cases, they must collaborate with academic researchers and medical institutions.

Although study protocols can either be drafted by the principal investigator (academic trials) or by the pharmaceutical company (industry trials), the studies share a common objective: establish new and better therapies that have the least amount of side effects. For industry trials, this has traditionally translated into drug approval submissions to Health Canada, provincial reimbursement and, ultimately, the generation of revenue. On the other hand, academic research is mainly interested in answering questions that are generally not addressed in industry trials, such as more convenient dosing schedules, more cost-effective drug combinations, mechanisms of the disease and evidence-based medicine to improve the health of patients.

Clinical research in myeloma has evolved substantially over the last few years. Disease site groups (such as foundations, medical institutions, voluntary groups or cooperative oncology groups) are now conducting clinical trials.

Common criteria used in myeloma trials

Some studies may use different definitions to describe how the disease is responding to the treatment and to accurately evaluate its efficacy. Be sure to check the study protocol for what the trial is using.

Below are common terms used by the International Myeloma Working Group (IMWG) to describe treatment response categories. The IMWG conducts research to improve outcomes for people with myeloma as well as creates consensus guidelines for the international myeloma community.

- **sCR (Stringent Complete Response):** Complete Response plus a normal ***free light chain*** ratio and an absence of clonal cells in the bone marrow.
- **CR (Complete Response):** No detectable monoclonal protein (M-protein or M-spike) in the serum or urine, disappearance of any ***soft tissue plasmacytomas (extramedullary tumours)*** and 5% or less of (cancerous) plasma cells in the bone marrow.
- **VGPR (Very Good Partial Response):** Serum and urine M-protein detectable by ***immunofixation*** (but not on ***electrophoresis***) or 90% or greater reduction in serum M-protein plus urine M-protein less than 100 mg per 24 hours.
- **PR (Partial Response)**: 50% or greater reduction in serum M-protein and a reduction in 24-hour urinary M-protein of 90% or more, or less than 200 mg per 24 hours. If serum and urine M-protein are not measurable, PR is defined as a 50% or greater decrease in the difference between involved and uninvolved free light chains. If free

light chains are unmeasurable, PR is defined as a 50% or greater reduction in (cancerous) bone marrow plasma cells, provided that the baseline percentage was 30% or more. If soft tissue plasmacytomas (extramedullary tumours) were present at baseline, a 50% or greater reduction in their size is also required.

- **MR (Minimal Response):** A reduction between 25-49% of serum M-protein and reduction in 24-hour urine M-protein by 50–89%. In addition to these criteria, if present at baseline, a reduction of 50% or greater in the size of the soft tissue plasmacytomas (extramedullary tumours) is also required.
- **SD (Stable Disease):** Not meeting the criteria for CR, VGPR, PR, MR, or progressive disease. SD is not recommended for use as an indicator of response, as the stability of disease is best described by estimating the time-to-progression.
- **PD (Progressive Disease):** Requires a 25% increase of one or more of the following:
  - Serum M-protein
  - Urine M-protein
  - If serum and urine M-protein levels are unmeasurable, the difference between involved and uninvolved FLC levels
  - If free light chains are unmeasurable, bone marrow plasma-cell percentage
  - Development of a new lesion(s)
  - If this is the only measure of disease, an increase of circulating plasma cells

Depending on the trial, additional common criteria that may be used include:

- **MRD (Minimal Residual Disease):** A very sensitive test that can measure minute levels of myeloma plasma cells in the bone marrow during and/or after treatment.
- **OS (Overall Survival):** Length of time from either the date of diagnosis or the start of treatment when the patient is still alive.
- **PFS (Progression-free Survival):** Length of time during and after the treatment that a patient is living with the disease without it progressing or getting worse.
- **TTP (Time to Progression):** Length of time from the date of diagnosis or the start of treatment until the disease starts to get worse or spreads to other parts of the body.

What happens after a clinical trial is completed?

Statistical analysis

After a clinical trial is done, the information that is collected during the study is carefully examined by the researchers with the help of a team of trained statisticians. The statisticians analyze the data and the trial ***endpoints*** are evaluated (e.g., optimal dose range or response criteria). If two or more treatments are being compared, the statisticians will also calculate whether there is a ***statistically significant*** difference between the experimental and control (standard of care) treatment arms to ensure that the observed difference did not occur by chance.

Research results

All safety information collected is compiled and analyzed to determine the risks associated with the experimental treatment. Results from clinical trials are often published in ***peer-reviewed*** scientific journals.

After early phase trials (Phase I or II), the researchers generally look at all the results to decide whether to move on to the next trial phase or whether to stop testing because the treatment was unsafe or ineffective. After Phase III trials, the researchers evaluate the compiled safety and efficacy data to determine whether the treatment being studied has the potential of being accepted as the new standard of care.

Health Canada approval of a new drug

Before a drug can be used in Canada, it must go through a rigorous approval process by Health Canada. Health Canada does not look solely at whether a new agent is safe, but at the balance between risks and benefits.

If the drug company's submission is approved, Health Canada will issue a Notice of Compliance (NOC) and give the drug a Drug Identification Number (DIN). This means the company is now allowed to market the new drug in Canada.

Once a new cancer drug is approved for use in Canada, the manufacturer must make a submission to stakeholders set up by the provincial and territorial Ministers of Health to

make recommendations as to whether new drugs should be covered under provincial formularies – the list of medications they will pay for.

If approved, the pan-Canadian Pharmaceutical Alliance (pCPA) will then conduct joint price negotiations with the drug manufacturers on behalf of the federal, provincial and territorial governments for new drugs in Canada.

Despite the national review processes that are in place, most publicly funded drug plans continue to make their own decisions as to which medications they will or will not list. As a result, the coverage of new treatments often varies across the country.

From approval to funding: The many steps before a drug is covered

Once a new cancer drug is approved for use in Canada, it goes through a health technology assessment (HTA) process that evaluates the clinical benefit versus the cost.

The manufacturer must make a submission to the Canadian Agency for Drugs and Technologies in Health (CADTH) pan-Canadian Oncology Drug Review for evaluation. The pan-Canadian Oncology Drug Review (pCODR) is an evidence-based cancer drug review process that assesses cancer drugs and makes recommendations to Canada's provinces and territories (except Quebec) to guide their drug funding decisions. In Quebec, the *Institut national d'excellence en santé* et en *services sociaux* (INESSS) issues recommendations and develops clinical practice guides in order to ensure a drug's optimal use.

It is during this stage of the evaluation process that patients, caregivers, patient organizations and clinicians have the opportunity to comment on the arrival of the drug under evaluation on the market. Through a form, it is therefore possible to share the point of view of patients, their relatives and clinicians in order to improve the relevance and quality of these assessments. This information will focus in particular on patients' experience of the disease or treatment, and the nature of their needs for the future.

In the next step of the process, the pan-Canadian Pharmaceutical Alliance (pCPA) conducts joint price negotiations with the drug manufacturers on behalf of the federal, provincial and territorial governments for new drugs in Canada. All new drugs receiving a positive recommendation from pCODR then undergo price negotiation through the pCPA.

Despite the national review processes that are in place, most publicly-funded drug plans continue to make their own decisions as to which medications they will or will not list. As a result, the coverage of new treatments often varies across the country. In some cases, even when a new drug is added to a ***formulary***, the decision as to whether to pay for it is made on a case-by-case basis. This special authorization process requires your physician to write a letter to the drug plan, explaining why you require this particular medication.

More information

Time-Limited Reimbursement Reviews and the Real-World Evidence (RWE) considered at CADTH

- Time-Limited Reimbursement Reviews and Real-World Evidence
- In alignment with international trends in evidence generation and drug approval policy, CADTH has worked with stakeholders like Myeloma Canada to develop Guidance for Reporting RWE and established a Time-Limited Reimbursement Review process. The Guidance for Reporting RWE establishes standards for researchers and reviewers to follow when gathering, analyzing, and assessing RWE in Health Technology Assessments and Reimbursement Reviews. Inclusion of RWE allows small populations like younger, or transplant ineligible patients to be better studied, and may provide a more holistic view of patients' experience with a treatment, particularly where there is no standard of care to compare the treatment to. The Time-Limited Reimbursement Review process creates a pathway for promising drugs at earlier stages of development to be reimbursed by public drug plans for a limited period of 3 years. To qualify, manufacturers must show CADTH they have a robust plan for continued study of the drug in a Phase III trial, and if granted a time-limited reimbursement recommendation, must submit the updated evidence to CADTH at the end of the 'limited' time. While only in their early stages, both initiatives have great potential to improve access to lifesaving treatments for people with myeloma.

More information

Access to new treatment options

Clinical trials provide access to new treatment options that have not yet been approved by Health Canada or covered by provincial governments. Once a new therapy is Health Canada approved, the provincial reimbursement process can take up to two years – sometimes even longer. During this time, you may obtain the drug through a clinical trial or:

- By paying for the drug out of your own pocket
- Through a private drug plan(many private plans also have formularies or lists of covered drugs)
- Through compassionate use programs (offered by pharmaceutical companies)

In some cases, drug manufacturers will pay for all or part of the drug if certain financial eligibility criteria are met. Some pharmaceutical companies have free services to help you search for coverage of specific drugs.

Know your options and health insurance coverage

To minimize your own out-of-pocket costs, some research may be necessary to ensure you have optimal access to new prescription medications.

- Some provinces only provide drug coverage for people who are 65 and older or on social assistance. Others may have a variety of plans, such as special coverage for those facing significant prescription drug costs. Drugs provided through cancer centres can also vary from province to province. Talk to your cancer team social worker, pharmacist, drug reimbursement advisor or call your provincial Ministry of Health to learn about all your options. If you have private health insurance or a drug plan at work, carefully review your benefits.
- If you are employed, meet with your Human Resources department or union representative to help you better understand your benefits. Ask your doctor what drugs you may need in the future and check to see if your plan covers them. If applicable, try to coordinate the benefits so any portion of a drug cost that is not paid for by one plan is applied to the next.
- Some private insurance plans require that you pay up-front and then apply for reimbursement. If this is a problem for you (e.g., you need a very expensive drug), ask your insurance company to allow your pharmacy to send the bill directly to them.
- Don't be afraid to advocate for yourself. For instance, if your employee health plan does not cover a certain drug, ask your employer or human resources manager if the company can make an exception in your case. Or ask your employer if it can waive the cap on your drug coverage.
- Find someone to work with you to advocate for the drug coverage you need. This person (family member, friend, etc.) can help continue to advocate for you even when you cannot.
- If you are refused coverage of a medication you need, appeal the decision. Sometimes the refusal may be the result of nothing more than faulty paperwork. Insurance companies will sometimes change their mind if you appeal.
- Some pharmaceutical companies have free services that will help you search for coverage of specific drugs. Sometimes a compassionate use program is offered to patients requiring the drug. Talk to your cancer care team or search online to see if you may be eligible for such a program.

Myeloma immunotherapy development in clinical trials

What is myeloma immunotherapy?

Myeloma immunotherapy are treatments that work by stimulating the body's ***immune system*** to recognize and eliminate myeloma cells. Due to the complex nature of an immune system response and its various components, there are many potential ways it can be influenced by immunotherapy treatments.

The earliest example of myeloma immunotherapy is allogeneic (donor) ***stem cell transplantation*** (also known as bone marrow transplant) because it uses the immune system of a healthy matching donor – i.e., a relative (usually a sibling) or matched unrelated donor to attack myeloma cells in the recipient. Today, the approach remains an active area of research that is generally undertaken under the supervision of a clinical trial setting with a small number of select patients.

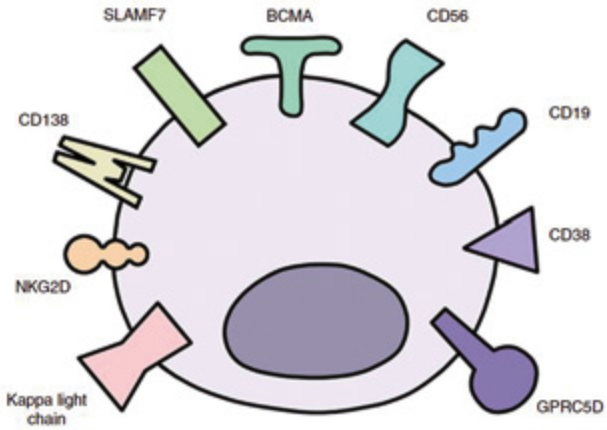
Antigen targets

For myeloma immunotherapy to work at its best, the goal is for the treatment to target antigens that are generally more numerous on the surface of myeloma cells, but not present on most healthy cells. Some antigens may also be on the surface of other cells, so they may not all be possible targets for myeloma immunotherapy.

Many new immunotherapy approaches have been developed to target the B-cell maturation antigen (BCMA) because BCMA is heavily expressed by nearly all myeloma cells but not by healthy plasma cells. There are also specific antigens on the surface of T-cells (e.g., CD3) that could be helpful to "recruit" ***T-cells*** and enhance myeloma cell destruction.

Figure 2 illustrates some myeloma cell antigen targets that have been studied or are being investigated (at the time of printing), in clinical trials.

Figure 2 – Myeloma cell antigen targets



For more information about myeloma immunotherapy, please refer to the Myeloma Canada website (www.myeloma.ca) or read Myeloma Canada's Myeloma Immunotherapy InfoGuide.

Ongoing research

Research is being conducted in all stages of myeloma – from precursor conditions like monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM) to newly diagnosed and relapsed/refractory myeloma. Studies are also examining the influence of genetic factors on disease progression and responses to various treatments, with the aim of creating more personalized treatment plans. Extensive research into several different cellular therapies like ***chimeric antigen receptor (CAR) T-cell therapy***, bi-specific or tri-specific antibody therapies, with varied genetic targets is underway. Furthermore, CAR ***natural killer (NK)*** cell therapies are being explored, a potential ready-to-use option that doesn't pose a risk of graft-versus-host disease. Researchers are also testing newer treatments in earlier lines of therapy to optimize treatment sequencing and maximize efficacy. This includes investigating different combinations of new and existing treatments.

New and emerging immunotherapies being studied in clinical trials

Several new immunotherapies are in development at this time. Some of them include:

- Belantamab mafodotin (Blenrep; belamaf) – an antibody-drug conjugate that targets BCMA on myeloma cells
- Elranatamab (PF-06863135; Elrexfio) – a bispecific antibody that targets BCMA on myeloma cells, as well as CD3 on T-cells

- Teclistamab (Tecvayli) – a bispecific antibody that targets BCMA on myeloma cells, as well as CD3 on T-cells
- Talquetamab (JNJ-64407564; Talvey) – a bispecific antibody that targets GPRC5D on myeloma cells, as well as CD3 on T-cells
- Cevostamab (BFCR4350A) – a bispecific antibody that targets FcRH5 on myeloma cells, as well as CD3 on T-cells
- ABV-383 – a bispecific antibody that targets BCMA on myeloma cells, as well as CD3 on T-cells
- Linvoseltamab – a bispecific antibody that targets BCMA on myeloma cells, as well as CD3 on T-cells
- Forimtamig (RO-7425781) – a bispecific antibody that targets GPRC5D on myeloma cells, as well as CD3 on T-cells
- AZD0305 – an antibody-drug conjugate that targets GPRC5D on myeloma cells
- SAR445514 – a trispecific antibody that targets BCMA on myeloma cells, as well as CD16a and NKp46 on NK cells
- SAR442257– a trispecific antibody that targets CD38 on myeloma cells, as well as CD28 and CD3 on T-cells

Additional myeloma therapies being studied in clinical trials

- Iberdomide (CC-220) – a cereblon E3 ligase modulator that targets cereblon
- Mezigdomide (CC-92480) – a cereblon E3 ligase modulator that targets cereblon
- Venetoclax (Venclexta) – a Bcl-2 inhibitor

Quality of life research

Due in part to the increasing patient involvement in research design and incorporation of patient reported outcomes measures, considerable efforts are being made to enhance the quality of life for patients undergoing treatment. This includes exploring options such as exercise or physiotherapy interventions, at-home administration of injectable treatments like bortezomib (e.g., Velcade), and wearable devices to detect immunotherapy side effects early so that they can be minimized.

Future myeloma research

Over time, several of the treatments discussed in this InfoGuide will be approved for the treatment of myeloma. Myeloma research is constantly evolving and increasing at an incredible rate. Newer, more personalized therapies are being developed that will increase future treatment options for people living with myeloma. Upcoming clinical trials will also continue to evaluate several multi-drug myeloma treatment approaches to determine the best combinations and optimal sequential use.

Myeloma research priorities in Canada

Myeloma Priority Setting Partnership (PSP)

Myeloma Canada's involvement in the Myeloma PSP reflects our commitment to support research that matters most to our community members living with, or otherwise impacted by this complex disease.

Started in the fall of 2019, the Myeloma Priority Setting Partnership (PSP) was a unique project that surveyed the Canadian myeloma community to determine their top 10 priorities for future myeloma research. A pan-Canadian committee consisting of Canadians living with myeloma, caregivers, and healthcare professionals worked together through the established James Lind Alliance (JLA) process to vet over 3,000 questions before arriving at the final top 10 myeloma research priorities. This exhaustive process included community surveys, analyses, and a consensus-building workshop.

There were many common themes that emerged from the bank of questions received, most of which centred around:

- improving the time and process for diagnoses;
- lifestyle;
- quality of life.

While the PSP focuses on the top 10 myeloma research priorities, we have safeguarded all questions for future consideration.

PSP research priorities

Here are the prioritized top 10 myeloma research questions identified by the Myeloma PSP:

1. How can we cure myeloma?
2. Are novel immunotherapies effective for the treatment of myeloma?
3. How can we improve the diagnosis (i.e., faster, less invasive) of myeloma, and what is the impact of earlier diagnosis on patient outcomes?
4. What are new treatments for myeloma patients that will improve life expectancy with fewer adverse side effects?

5. How can we personalize a patient's treatment based on their type of myeloma and genetic profile, and what is the impact of personalized medicine on treatment efficacy and disease outcomes?
6. How can we prevent bone deterioration and/or repair bones that have been damaged without negative side effects or surgery?
7. How can we safely reduce, cycle, or stop the use of medications to reduce the side effects of treatment and maintain control over myeloma?
8. How can we reduce or manage the short- and long-term effects of myeloma treatment?
9. What is the most effective way (i.e., drug combinations, sequence, frequency, and intensity) to treat refractory, relapsed, and drug-resistant myeloma?
10. Can we develop treatments specifically for high-risk or aggressive myeloma that will improve outcomes for these patients?

Glossary

Antibodies (immunoglobulins): Protein that are produced by certain white blood cells (plasma cells) to fight infection and disease in the form of antigens such as bacteria, viruses, toxins or tumours. Each antibody can bind only to a specific antigen. The purpose of this binding is to help destroy the antigen. Antibodies can work in several ways, depending on the nature of the antigen. Some antibodies disable antigens directly. Others make the antigen more vulnerable to destruction by other white blood cells. Antibodies are Y-shaped molecules that have heavy and light chains (portions). These portions contain specific binding sites that attach to bacteria or viruses, ultimately leading to their destruction thereby protecting against disease.

Bone marrow: The soft, spongy tissue in the centre of bones that produces white blood cells, red blood cells and platelets.

Chimeric antigen receptor (CAR) T-cell therapy: Typically a one-time treatment that uses T-cells. T-cells are collected from a person's blood by pumping it through a machine that separates the T-cells from the rest of the blood. The collected T-cells are then genetically modified in a lab to express a CAR receptor protein on its surface that can better recognize an antigen on the surface of the myeloma cells to kill them more efficiently.

Clinical trials: Research studies done with patients to evaluate new treatments or new ways of combining and administering existing treatments. By testing new drugs or combinations of drugs, each study is designed to find better ways to treat the disease, as well as improve quality of life and answer scientific and clinical questions. The overall goal of conducting clinical trials is to improve patient care and outcomes.

Compassionate access: In certain situations, pharmaceutical companies offer compassionate access programs that provide a drug that is approved by Health Canada but not yet reimbursed to groups of patients who have no more options in terms of authorised therapies and who cannot enter clinical trials.

Health Canada's Special Access Programme allows practitioners to request access to drugs that are unavailable for sale in Canada. This access is limited to patients with serious or life-threatening conditions on a compassionate or emergency basis when conventional therapies have failed, are unsuitable, or are unavailable.

Contract research and site management organization: Provides research support services for pharmaceutical, biotechnology and medical device companies (study

sponsors), as well as government institutions, foundations, and universities. A CRO can manage/lead the company's clinical trials and its related duties and functions. They can help companies reduce the time it takes to conduct a trial and allow for cost savings by eliminating the need for additional infrastructure, office space and staff. CROs are also legally liable for the obligations they assume.

Site management organizations (SMOs) provide research support to individual sites/ investigators managing many regulatory obligations such as preparation/maintenance of cases and ensuring compliance institutional review board reviews and informed consent. Although SMOs can assume many of investigator duties, they are not legally liable for the obligations they assume and remain the responsibility of the investigator.

Drug Identification Number (DIN): A DIN is a unique computer-generated eight-digit number assigned by Health Canada to a drug product before it is allowed to be marketed/sold (in dosage form) in Canada. It lets the user know that the product has undergone and passed a review of its formulation, labeling and instructions for use. The DIN is located on the label of all prescription and over-the-counter drug products and also helps with the follow-up of products on the market, recall of products, inspections, and quality monitoring.

Electrophoresis: A laboratory test in which a patient's serum (blood) or urine molecules are subjected to separation according to their size and electrical charge. For myeloma patients, electrophoresis of the blood or urine allows both the calculation of the amount of myeloma protein (M-protein) as well as the identification of the specific M-spike characteristic for each patient. Electrophoresis is used as a tool both for diagnosis and for monitoring. There are two types of electrophoresis:

- Serum protein electrophoresis (SPE or SPEP)
- Urine electrophoresis (UPE or UPEP)

Endpoint: In a clinical trial, an endpoint generally refers to an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. Survival, improvements in quality of life, relief of symptoms and disappearance of a tumour are examples of endpoints that cab be included in the study objectives.

Formulary: List of prescription drugs that can be prescribed by practitioners. Formularies are maintained by an expert drug advisory committee and they can contain summaries of pharmacological information as well as administrative and regulatory information regarding prescribing and dispensing. National formularies generally concentrate on available and affordable drugs; however, formularies are also frequently created for different levels of healthcare (i.e., provincial), different sectors and for individual hospitals.

Free light chain: The light chain portion of an M-protein (monoclonal protein, paraprotein, M-spike) that is circulating in the blood in a free (unbound) state. Free light chains can be measured with a sensitive test, the Freelite® assay.

Health technology assessment: A comprehensive evaluation of the clinical effectiveness, cost-effectiveness, and the ethical, legal, and social implications of health technologies on patient health and the health care system.

Immune system: The complex group of organs and cells that produce antibodies to defend the body against foreign substances such as bacteria, viruses, toxins, and cancers.

Immunofixation: A specialized type of electrophoresis that can identify the type of monoclonal paraprotein or M-protein that makes up an M-spike (i.e., whether it is IgG, IgA, kappa (κ) or lambda (λ)). This immunoelectrophoresis test can be conducted on the blood (serum) or the urine.

Inclusion and exclusion criteria: Characteristics that qualify or disqualify prospective volunteers from participating in a clinical trial. These criteria may include factors such as age, sex, type and stage of disease, previous treatment history, presence/absence of other health conditions, etc.

Intravenously: Into/within a vein. The medication (solution) is administered directly into the venous circulation via an intravenous (IV) drip, syringe or catheter (central line).

M-protein (monoclonal protein, paraprotein, or M-spike): Also known as myeloma protein. These are antibodies or parts of antibodies found in unusually large amounts in the blood or urine of myeloma patients. M-spike refers to the sharp pattern that occurs on protein electrophoresis when an M-protein is present.

Maintenance therapy: A prolonged, low-dose, form of treatment given to myeloma patients after an autologous stem cell transplant. The goal of maintenance therapy is to reduce the risk of disease progression for as long as possible while maintaining a favourable quality of life.

Natural killer (NK) cells: These cells recognize and destroy cells that have been infected by viruses or changed by cancer, are responsible for tumour surveillance and can induce strong responses to tumours by releasing cytokines, and do not need to recognize a specific antigen to function.

Notice of Compliance: A notification issued by Health Canada indicating that a manufacturer has complied with specific sections of the Food and Drug Regulations following the satisfactory review of a submission.

Parent company: A company that controls one or more small businesses (subsidiaries).

Peer-reviewed: Evaluation of scientific, academic, or professional work by others working in the same field.

Plasma cells: Special white blood cells that produce antibodies. The malignant cell in myeloma. Normal plasma cells produce antibodies to fight infection. In myeloma, malignant plasma cells produce large amounts of abnormal antibodies that lack the capability to fight infection. The abnormal antibodies are the monoclonal protein, or M protein. Plasma cells also produce other chemicals that can cause organ and tissue damage (ie, anemia, kidney damage and nerve damage).

Principal investigator: The person that is in charge of a clinical trial at a given site. They prepare (only for investigator-initiated trials) and carry out the clinical trial study protocol/plan, recruit and look after research patients, and report the results of the trial. They are often referred to as the PI.

Side effects (adverse events): Problems that occur due to drugs used for disease treatment. Common side effects of cancer therapy are fatigue, nausea, vomiting, decreased blood cell counts, hair loss and mouth sores.

Smouldering myeloma: Also referred to as asymptomatic myeloma. It is a precursor state to symptomatic or active myeloma. In this state, patients do not have anemia, renal

failure, hypercalcemia, bone lesions or myeloma-defining events. Abnormal plasma cells may make up 10-60% of the bone marrow, serum M-protein is greater than 30 g/L, and urinary M-protein is equal to or greater than 500 mg per 24 hours. Because the disease is not yet active, asymptomatic myeloma is usually observed but not treated. Clinical trials are presently studying whether patients with high-risk asymptomatic myeloma should be treated before the onset of active myeloma.

Soft tissue plasmacytomas (extramedullary tumours): A collection of plasma cells found in a single location rather than diffusely throughout the bone marrow, soft tissue, or bone.

Sponsor: An individual, institution, company or organization that is responsible for initiating, managing and financing the clinical trial. Sponsors do not carry-out the study.

Statistically significant: The likelihood that the relationship between two or more variables (ie, results of a data set) is caused by something other than random chance.

Stem cell transplantation: A procedure where blood-forming stem cells are administered intravenously to a patient to replace stem cells that were intentionally destroyed by radiation or high-dose chemotherapy treatment. Patients may receive their own stem cells (autologous transplant) or stem cells from a donor (allogeneic transplant). An autologous transplant is the standard of care and most commonly used therapeutic approach for newly diagnosed transplant-eligible patients with myeloma. Although called stem cell "transplantation", there is no actual organ removed from a donor to a recipient. Because stem cells were traditionally collected directly from the bone marrow rather than from the circulating blood, the procedure was originally referred to as a bone marrow "transplant".

Study protocol (written plan): A document that describes and defines each step of the clinical trial, as well as the study's background, rationale, objectives, design, methodology, statistical considerations, etc. The protocol includes a specific plan to ensure the safety and health of the trial participants and all of the study investigators are expected to strictly abide by to it. This allows the data to be shared and combined across all of the study's investigators/sites. The format and content of clinical trial protocols sponsored by pharmaceutical, biotechnology or medical device companies in Canada (along with other countries) have been standardized to follow guidelines issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Subcutaneously: The medication is pushed into the body with the use of a syringe and needle.

T-cells: These lymphocytes recognize specific antigens on harmful cells, bind to harmful cells to surround and disable them and can transform into memory cells for long-lasting immunity.

Therapeutic value: Response(s) after a treatment that are judged to be desirable and/or beneficial. A treatment that has therapeutic value can treat an illness and improve a person's health.

Translational research: Preclinical, evidence-based or disease-targeted research that looks at determining (or "translating") the relevance of innovative scientific findings to the treatment of disease. Also called bench research.

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