Clinical Trials as a Treatment Option
Introduction

Over the past 15 years, research has increased our understanding of myeloma and its underlying disease process. This has led to the development and approval of new treatments with novel therapies such as thalidomide (Thalomid®), bortezomib (Velcade®), lenalidomide (Revlimid®) and, most recently, pomalidomide (Pomalyst®), carfilzomib (Kyprolis®), daratumumab (Darzalex®) and ixazomib (Ninlaro®). These new drugs have extended the lives of many patients living with myeloma and they would not be available without the participation of patients in clinical trials.

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 treatment option for each patient's specific situation.

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 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.

Some of the more technical or unusual words appear in bold the first time they are used and are explained in the glossary on page 20.

As you read through this InfoGuide, you may refer to the “More Information” and “Did You Know?” boxes to learn more about selected topics.

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

Disclaimer

The information in this InfoGuide is not meant to replace the advice of your medical team. They are the best people to ask if you have questions about your specific diagnosis, treatment and medical/social situation.
About Myeloma Canada

Myeloma Canada is a registered non-profit organization created by, and for, people impacted by multiple myeloma. As the only national organization exclusively devoted to the Canadian myeloma community, Myeloma Canada has been making myeloma matter since its founding in 2005.

Working with leading myeloma researchers and clinicians as well as other cancer organizations and local support groups across Canada and internationally, Myeloma Canada seeks to strengthen the voice of the Canadian myeloma community and improve the quality of life of myeloma patients, their caregivers and families through education, awareness, advocacy, clinical research and community engagement.

Myeloma Canada’s goals are to:

- Provide educational resources to patients, families and caregivers
- Increase awareness of the disease and its effects on the lives of patients and their families
- Facilitate access to new therapies, treatment options and healthcare resources
- Advance clinical research and promote access to new drug trials in Canada
- Empower patients and caregivers through community engagement

This InfoGuide is dedicated to helping patients and families who are living with myeloma better understand clinical trials and the role they can play to help advance clinical research and improve outcomes.

For more detailed information about myeloma and living with the disease, you can refer to Myeloma Canada’s educational publications:

- Multiple Myeloma Patient Handbook
- Myeloma Bone Disease InfoGuide
- Understanding Your Blood and Blood Tests InfoGuide
- Myeloma and the Kidney InfoGuide

To order free copies, send an e-mail to contact@myeloma.ca or call 1-888-798-5771 toll free.

Visit www.myeloma.ca to download Myeloma Canada’s educational publications or to find a support group in your area.
Born from an idea to advance scientific knowledge and improve patient outcomes through collaboration and knowledge sharing, the MCRN has evolved into a pan-Canadian group of dedicated scientists, investigators and clinicians who share a common vision: Working together for a world where myeloma is no longer a fatal disease.

The MCRN is the first and only national academic myeloma research group bringing together Canada’s leading myeloma researchers and clinicians from 25 centres in nine provinces across the country. The MCRN brings meaningful value through its network of internationally recognized investigators who understand the importance of sharing their expertise to accelerate patient-focused, leading-edge myeloma research and technologies to identify new treatments and make them available through its member institutions in both large urban and smaller communities across Canada.

The MCRN’s mission is to:

- Conduct innovative Phase I and II clinical trials and \textbf{translational research} in a collaborative manner to improve patient outcomes in multiple myeloma
- Publish evidence-based and peer-reviewed consensus statements on the diagnosis and treatment of myeloma
- Develop a nationwide myeloma patient database
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Clinical Trials as a Treatment Option for Myeloma

Overview

Myeloma is a cancer that affects plasma cells, a type of white blood cell that is made in the bone marrow by “blood-forming” stem cells. Plasma cells produce antibodies (immunoglobulins) that fight infection; therefore, they are an important component of the body’s immune system.

The production of plasma cells is a controlled process. When plasma cells age and/or become damaged, they normally die and new plasma cells take their place. In a person with myeloma, this process “breaks down” resulting in the uncontrolled growth of abnormal plasma cells, also known as myeloma cells. The myeloma cells can have a negative effect on different parts of the body and interfere with the production of other types of blood cells by “crowding out” the bone marrow. Furthermore, myeloma cells overproduce one type of antibody, known as an M-protein (also referred to as monoclonal protein, paraprotein, or M-spike). Due to the overproduction of myeloma cells and M-protein, several characteristic health problems can occur:

- Elevated blood calcium (hypercalcemia)
- Kidney damage
- Low hemoglobin (anemia)
- Bone pain and/or fractures (lesions)
- Frequent or recurring infections
- Fatigue/weakness

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.
Based on the specifics of your myeloma diagnosis, 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. The medical team may recommend turning to new drugs or combinations of treatments that are only available through participation in clinical trials. Often, the drugs or combinations of treatments being studied in clinical trials are not yet approved by Health Canada and, therefore, unavailable to patients, except through a clinical trial. Clinical trials may also provide access to drugs or combinations of treatments that are approved by Health Canada but not covered by provincial governments.

**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 that is designed to look like the drug being tested in some clinical trials. This is done to account for a “placebo effect,” which is a perceived psychological effect that does not reflect the efficacy of the actual drug. In general, it is unethical to receive no treatment or a placebo on its own in studies that treat cancer. At the very least, participants are given the approved standard of care treatment with or without the placebo.

Arms
The specific treatment groups of clinical trials.

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

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

Cross-over option
A cross-over option may be available 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 provide the option to “cross-over” to the experimental arm and receive the treatment being studied. **Note**: Not all studies allow for cross-over; this will be told to you at the beginning of the study, or you can ask your doctor or nurse before you sign an informed consent form (see page 9).
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, half of the participants receive the treatment being studied (experimental arm), while the other half receives the standard of care treatment alone or with placebo (control arm).

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

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Experimental Arm</th>
<th>Control Arm</th>
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<tr>
<td>Open label</td>
<td>Treatment being studied</td>
<td>Standard of care treatment</td>
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<tr>
<td>Blinded</td>
<td>Treatment being studied</td>
<td>Standard of care treatment + Placebo</td>
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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 economics 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 the side effects felt and the frequency that supportive medications (eg, painkillers) were taken.

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 risks and benefits of the study. They are usually tested and assessed more frequently due to the necessity of monitoring their safety. Specialized doctors, nurses, and other research staff will closely monitor them throughout the trial, and for a long period after the trial is finished. This is done to monitor any potential long term or “latent” effects of the study treatment.

MYTH: Clinical trials are expensive for patients

Most clinical trials are not financially burdensome. In fact, physicians will sometimes recommend participation in clinical trials to reduce costs for the patient. In most cases, hospitals, private organizations or pharmaceutical companies conduct trials at no expense to the patient. In certain provinces, paying out of pocket for any expenses incurred during a clinical trial is deemed unethical by their ethics boards.

Did You Know?

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 at the national or international (global) level.

Because clinical trial 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 13) clinical trials are reviewed and monitored 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 undergo periodic regulatory approvals to track and evaluate ethical implications, participant safety, efficacy of the study treatment and the quality of the data that are being produced. These checks are in place to demonstrate compliance of the sponsor/investigator with the standards of “Good Clinical Practice”.

Safety & Monitoring

In clinical trials there are many unknowns, including short-term and long-term side effects of the drug being evaluated and how well the participant will respond to the treatment. The numerous safeguards that are in place, together with close monitoring, help minimize potential risks. Strict regulations 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 ongoing medications will not interfere with the study treatment.

Response to the experimental treatment is carefully followed by the research team. Due to this, it may be possible that participants receive more tests during the trial and have more doctor visits compared to the regular care setting.
### Safeguards That Ensure Good Clinical Practice

To ensure good clinical practice, all entities 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 14 for more information), supervise the treatment plan and ensure that all of all approvals (eg, ethics, hospital, Health Canada) have been received prior to starting a trial. Many other participating 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 founded 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 with the IRB/REB or its parent company. The IRB/REB’s overarching mission is to protect human research participants and provide rapid, thorough ethical reviews that can withstand the scrutiny of regulatory bodies such as Health Canada. As part of its mandate, it can decide how often to review the trial once it has begun and stop a clinical trial if:

- The protocol is not followed
- It appears to be causing unexpected harm
- A new intervention is shown to be more effective

**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 all trial results, tests and safety (all Phase III trials and some Phase I and II trials)
- Ensure the data that are captured are complete

If the treatment being studied shows a clear advantage, the DSMB can recommend that a trial end early and proceed to the approval process. A negative recommendation for a trial to end 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

There are certain conditions and requirements that you must meet in order to be able to participate in a particular study. Both the inclusion criteria (conditions that all participants must meet) and exclusion criteria (conditions that all participants cannot have) are a vital part of the research plan to get credible and consistent results. Examples of eligibility criteria may include: 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 Document

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

Once you have read and agree with the conditions outlined in the informed consent document, you will be asked to sign it to confirm your participation in the study. If you have any questions about the trial and the informed consent, you are encouraged and have the right to consult your doctor or a member of the clinical trial team before and/or during 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 with anyone you feel appropriate, and take as long as you need to decide whether to participate.

Did You Know?

Dropout

Informed consent is voluntary. If you do not choose to go on the trial, your doctor or nurse will discuss other treatment options with you. You are free to withdraw from the study completely without providing a reason. You may also refuse particular treatments or tests; however, please note that you may be withdrawn from the trial, depending on which treatments or tests you are consistently refusing. You must always discuss any deviations from the protocol with your study team.
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 and whether they might be better or worse than being 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
- If the information learned during the study might affect your safety

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

Did You Know?

Clinical Trial Outcomes Make a Difference

We can gain insights and answers 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?
■ 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 and the advantages can outweigh the disadvantages. Before agreeing to participate, you must learn about the possible risks of entering a trial and what other options are available to you. Potential participation should be discussed in depth with your healthcare team.

Although the main benefit of participating in clinical trials is access to new treatment options that can be potentially life-saving/extending and/or significantly improve quality of life, people participate in clinical trials for a variety of reasons. Whether a person is newly diagnosed or has relapsed or refractory disease, there are a number of additional advantages that come with participating in clinical trials compared to regular care. These include:

- Close monitoring of any potential side effects by the clinical trial team
- Care provided by a leading physician in the field of myeloma research
- Helping accelerate new drug approvals and/or their reimbursement through the evidence generated from the trial
- Helping researchers find better treatment options, advance myeloma research and improve the way patients will be treated in Canada, and at your cancer centre

However, there are some potential disadvantages of participating in clinical trials, related to the treatment being studied. The treatment may:

- Not work for a specific person (although the same could be said for any treatment)
- Be ineffective or less effective than the current standard of care treatment
- Result in unpleasant, serious or unknown side effects
- Result in extended time being spent at the hospital or clinic, thus less time for work and with family and friends

Depending on where you live and the study protocol (written plan), another important consideration may be the amount of time and cost related to travelling for treatments and/or clinic visits.
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.
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 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. For instance, the Myeloma Canada Research Network (MCRN) carries out clinical and translational myeloma research throughout Canada. This has allowed for a more constructive partnership with industry and patients, leading to improved study design, better site selection and enhanced monitoring/reporting processes. Moreover, the MCRN National Multiple Myeloma Database has enabled the exploration of additional scientific questions and helped in the generation and evaluation of new clinical hypotheses.
## Summary of Clinical Trial Phases

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| I     | - Usually 15 to 30 people  
      | - To find the safe maximum tolerated dose (MTD)  
      | - To decide how the treatment should be given (e.g., orally or **intravenously**)?  
      | - To observe how the treatment affects the human body |
| II    | - Usually less than 100 people  
      | - Uses the maximum tolerated dose (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” |

### More Information

**Find Clinical Trials in Canada**

To search for clinical trials in Canada, please visit the following websites:

1. [www.myeloma.ca/findtrials](http://www.myeloma.ca/findtrials)
   - Find myeloma trials that are recruiting in Canada by disease stage and postal code.

2. [www.canadiancancertrials.ca](http://www.canadiancancertrials.ca)
   - A Canadian website that allows you to search by cancer type and location.

3. [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
   - This website is a service provided by the US National Institute of Health.

4. [https://health-products.canada.ca/ctdb-bdec/index-eng.jsp](https://health-products.canada.ca/ctdb-bdec/index-eng.jsp)
   - Health Canada’s Clinical Trials Database
Common Criteria Used in Myeloma Trials

When undergoing treatment for your myeloma, you may hear terms such as “complete response” or “partial response” used to describe how the disease is responding to the treatment and to accurately evaluate its efficacy. Some studies may use different definitions for this evaluation so be sure to check the study protocol for what the trial is using. The most common response criteria, developed by the International Myeloma Working Group, are:

- **sCR (Stringent Complete Response):** Complete Response (see description below) plus a normal free light chain ratio and an absence of myeloma plasma cells in the bone marrow.

- **CR (Complete Response):** No detectable monoclonal protein (M-protein or M-spike) in the blood or urine, disappearance of any soft tissue plasmacytomas (extramedullary tumours) and 5% or less of myeloma plasma cells in the bone marrow.

- **VGPR (Very Good Partial Response):** Detectable blood and urine M-protein by immunofixation (but not on electrophoresis) or 90% or greater reduction in blood M-protein plus urine M-protein less than 100 mg per 24 hours.

- **PR (Partial Response):** 50% or greater reduction in blood M-protein and a 90% or greater reduction in 24-hour urine M-protein (or less than 200 mg per 24 hours). If blood and urine M-protein are not measurable, PR is defined by additional criteria (ask your healthcare team). If soft tissue plasmacytomas (extramedullary tumours) were present, a 50% or greater reduction in their size is also required.

- **MR (Minimal Response):** A reduction between 25-49% of blood M-protein and reduction in 24-hour urine M-protein by 50–89%. If soft tissue plasmacytomas (extramedullary tumours) were present, a 50% or greater reduction in their size is also required.

- **SD (Stable Disease):** Not meeting the above criteria or progressive disease (see below). 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):** Generally speaking, a 25% or greater increase in one or more of the several features of myeloma (serum and urine M-protein, free light chain ratio, myeloma plasma cells) or the appearance of a new bone lesion (other criteria apply for existing lesions; ask your healthcare team). PD can also be defined as an increase of 50% or greater in circulating plasma cells if it is the only measure of disease.

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.
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 (eg, 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. Furthermore, all of the 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 of 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

Just because a new therapy has been shown to be effective in a Phase III trial doesn’t mean that it is automatically available in Canadian hospitals, clinics or pharmacies. 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 clinical benefit of the new treatment is proven to be statistically significant over the standard of care treatment and its potential therapeutic value outweighs the risks associated with its use (eg, side effects or toxicity), the pharmaceutical company or sponsor will apply to the Health Products and Food Branch (HPFB) of Health Canada to have the drug officially approved for use in Canada.

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. In some cases, Health Canada may award a Notice of Compliance with Conditions (NOC/c). A drug awarded with a NOC/c is given a DIN but the sponsoring company must agree to special conditions or requirements, such as additional research or professional and patient education.
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.

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 publically-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.

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 care 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.
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.

**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 can 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 (ie, 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: An 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.

Immunofixation: A specialized type of electrophoresis that can identify the type of monoclonal paraprotein or M-protein that makes up an M-spike (ie, 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.

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.

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.

**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 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).

**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.
Make Myeloma Matter

Every year, Myeloma Canada provides information to thousands of people with myeloma and their families and caregivers, and helps many more by providing programs and services such as the annual Myeloma Canada National Conference, Patient and Family InfoSessions, the *Myeloma Matters* newsletter and webinars.

That is why we need your help. We depend on support and generous donations from people like you to provide support to myeloma patients, their families and their caregivers. All donations are greatly appreciated and allow us to continue our vital work.

**Ways You Can Help**

**Donate**

You can make your donation online at [www.myeloma.ca](http://www.myeloma.ca), over the phone by calling toll-free at 1-888-798-5771, or by mailing a cheque payable to Myeloma Canada to:

Myeloma Canada  
1255 Trans-Canada Highway, Suite 160  
Dorval (Quebec)  
H9P 2V4

**Fundraise**

There are other ways you can support Myeloma Canada, such as taking part in the annual Multiple Myeloma March held in cities across Canada, or by fundraising for Myeloma Canada in your local community. When so much about myeloma is beyond the control of the people that it affects and those who care for them, fundraising can be a rewarding and fun way of doing something positive for yourself and for others affected by myeloma.

Contact the fundraising team toll-free at 1-888-798-5771 for more information, or visit [www.myeloma.ca](http://www.myeloma.ca).
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Myeloma Canada publications are extensively reviewed by patients and healthcare professionals prior to publication.

Sincere thanks to the fundraising efforts of the Canadian myeloma community who make myeloma matter by helping to advance Myeloma Canada’s objectives of education, awareness, access and research.

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