Understanding Clinical Trials
Founded in 1990, the International Myeloma Foundation (IMF) is the first and largest organization focusing specifically on multiple myeloma. The IMF’s reach extends to more than 525,000 members in 140 countries worldwide. The IMF is dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure through our four founding principles: Research, Education, Support, and Advocacy.

**RESEARCH** The signature project of the IMF’s Research division is the Black Swan Research Initiative®, a groundbreaking and collaborative effort to develop the first definitive cure for myeloma. Each year, the IMF also awards Brian D. Novis Grants, which promote research for better myeloma treatments, management, and practices in the field. In addition, more than 200 leading myeloma researchers comprise the IMF’s International Myeloma Working Group (IMWG), a research body that has developed myeloma guidelines that are followed around the world. Finally, the IMF’s Nurse Leadership Board (NLB), comprised of nurses from leading myeloma treatment centers, develops recommendations for the nursing care of myeloma patients.

**EDUCATION** The IMF Patient & Family Seminars and Regional Community Workshops are held around the world to provide up-to-date information presented by leading myeloma specialists and researchers directly to patients and their families. The IMF’s library of more than 100 publications, for patients and caregivers as well as for healthcare professionals, is updated annually and available free of charge. Publications are available in more than 20 languages.

**SUPPORT** The IMF’s InfoLine is staffed by information specialists who answer myeloma-related questions and provide support via phone and email to thousands of families each year. In addition, the IMF sustains a network of more than 150 myeloma support groups and offers training for the hundreds of dedicated patients, caregivers, and nurses who volunteer to lead these groups in their communities.

**ADVOCACY** The IMF’s Advocacy team has educated and empowered thousands of individuals who make a positive impact each year on issues critical to the myeloma community. Working in the US at both federal and state levels, we lead coalitions to advocate for parity in insurance coverage. We also represent the myeloma community’s interests before the US Congress and agencies such as the National Institutes of Health, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the Veterans Administration. Outside the US, the IMF’s Global Myeloma Action Network (GMAN) works to help patients gain access to treatment.

Learn more about the ways the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure. Contact us at 818.487.7455 or 800.452.CURE, or visit myeloma.org.

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What you will learn from this booklet

The IMF’s Understanding series of booklets is designed to acquaint you with treatments and supportive care measures for multiple myeloma (which we refer to simply as “myeloma”). Words in bold+blue type are explained in the “Terms and definitions” section at the end of this booklet, as well as in a more complete compendium of myeloma-related vocabulary, the IMF’s Glossary of Myeloma Terms and Definitions, located at glossary.myeloma.org.

Myeloma is a cancer that is not known to most patients at the time of diagnosis. To be empowered to play an active role in your own medical care and to make good decisions about your care with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments. The information in this booklet will help you in discussions with your healthcare team. The more information you have about resources that are available to you, the better and more fruitful that discussion will be.

At some point in the cancer care continuum, clinical trials can be a treatment option for many people with cancer. Clinical research in myeloma has become a robust field, with the National Cancer Institute (NCI) website cancer.gov listing well over 1,000 clinical trials for myeloma. Whether or not to participate in a clinical trial is one of the critical decisions you and your oncologist may have to make in the course of your cancer treatment.

What is a clinical trial?

Clinical trials are research studies of new treatments that involve patients. By testing new drugs or combinations of drugs, each study is designed to find better ways to prevent, detect, diagnose, or treat cancer, to improve the quality of life of the patient, and to answer scientific questions.

The overall goal of conducting clinical trials is to improve cancer care, particularly overall survival (OS).

Many hospitals now take part in clinical trials, which are only undertaken after laboratory studies have outlined the potential safety of a new treatment or procedure, and it has been found to have the potential to work better than existing methods.

Clinical trials vary greatly in size, from a single researcher in one hospital or clinic to an international multicenter study with hundreds of participating researchers on several continents. The number of patients in a test can range from a few individuals to several thousand.

What are the phases of a clinical trial?

Phase I clinical trial

A phase I trial is designed to determine the maximum-tolerated dose (MTD) of a new drug or a new combination of drugs that has never been tried in humans. It is usually the first human testing of a new treatment, although in phase I trials of combination therapies, the individual elements may already have been well-tested. Generally, patients in phase I trials will have advanced cancer that is refractory to any standard treatment. In a typical phase I trial, successive groups (“cohorts”) of three to six patients are given the treatment. All patients in a cohort get the same dose. The first cohort typically gets a very low dose, and the dose is increased in each subsequent cohort until a set number of patients experience dose-limiting toxicity (DLT). The dose level used for the previous cohort is then taken to be the MTD. This MTD is then used in a phase II trial.

Phase II clinical trial

A phase II trial is designed to determine the response rate of a new single agent or combination therapy that has already been tested in phase I trials. Typically, 14 to 50 patients with one type of cancer are treated to see how many have a response. Patients are usually required to have advanced cancer that is refractory to any standard treatment. In addition, they must have measurable disease. If results from a phase II trial are promising enough, the treatment may then be tested in a phase III trial. If the results are obviously much better than the standard treatment, then it may not be necessary to do a phase III trial, and the treatment may become standard based on phase II trial results.

Phase III clinical trial

The end point of a phase III trial is usually survival or progression-free survival (PFS). Phase III trials are usually randomized, so patients don’t choose which treatment they receive. A typical phase III trial can have 50 to thousands of patients. Phase III trials are usually designed so that patients are separated into groups called “arms” to compare one or more therapies to a standard treatment. The patients who receive the experimental therapy are in the “experimental arm,” and the patients who receive the standard treatment are in the “control arm.” Often, neither the patients nor the researchers conducting the trial know to which arm any patient has been randomized, and thus the term “double blind” is used. Randomized trials are designed to produce data that is truly unbiased from expectations. Sometimes the patients in one arm of a study do much better than the patients in the other arm, and then the study is “unblinded” and the patients are all given the better therapy.
Some phase III trials compare a new treatment that has had good results in phase II trials with an older, well-known, standard treatment. Other phase III trials compare treatments that are already in common use. Some treatments in phase III trials may be available outside the clinical trial setting. The best measure of the success of a therapy is overall survival, but it can take years or even decades to follow patients on a clinical trial to see how long they survive. In order to find a shorter measure of a drug’s efficacy, most trials for myeloma therapies use PFS.

**Phase IV clinical trial**

Even after a drug has been approved by the US Food and Drug Administration (FDA) for use in a particular indication, there may be need for additional safety surveillance and ongoing technical support. Post-FDA-approval studies (also known as phase IV trials) may be required by regulatory authorities or may be undertaken by the sponsoring company for a variety of reasons, such as finding a new market, testing for interactions with other drugs, or on certain population groups who are unlikely to join a trial themselves. The safety surveillance is designed to detect any rare or long-term side effects over a larger patient population and longer time period than what is possible during the phase I to phase III clinical trials.

**What is informed consent?**

Informed consent is a vital part of the research process and is mandated by law for every participant in every research study. It demands that clinical investigators educate potential study subjects to ensure that a truly informed decision to participate in a clinical trial is voluntary and not coerced, and that patients have a good knowledge base and understand what participating in the clinical trial involves. An informed consent is a document that explains every part of the clinical trial, but it is also the discussion between a patient, physician, and other members of the healthcare team that must take place before the document is signed. The consent form is written in words that are geared toward non-medical readers, and it explains what the trial consists of in detail. It demands that a doctor assume responsibility for educating a patient about a trial, alternatives to doing that trial, and the potential risks of the drugs involved. It also requires that a patient must assume responsibility for asking questions and agreeing to participate in a trial based not on fear or intimidation, but on facts.

**Medical progress and patient safety**

Clinical trials are used to further test new medications and therapies on human subjects. Clinical trials are performed using protocols that adhere to accepted standards of patient safety, informed consent, and data interpretation. Strict regulation of clinical trials helps to ensure that the balance between medical progress and patient safety is carefully maintained.

**When is the right time to participate in clinical trials?**

Clinical trials have the opportunity to offer new therapies for myeloma that are not FDA-approved. In clinical trials, researchers don’t know if the new method will be better than standard therapy for patients who are being treated now. What researchers do know is that some clinical trials will result in better treatments for patients in the future.

Taking part in a clinical trial is voluntary. Not all clinical trials are right for every patient. Potential participation in a clinical trial should be discussed in depth with your physician and healthcare team. Before agreeing to participate, patients must learn about possible risks of the therapy being studied and what other options for treatment are available.

**What does “eligibility criteria” mean?**

In clinical trials, there are certain conditions and requirements that patients must meet in order to be deemed suitable for a research study. When all study subjects meet the same eligibility criteria, it provides researchers with consistent data needed to answer the question of the research study.

Eligibility requirements are based on the type of research study or clinical trial. Examples of eligibility may include: age, performance status, type and stage of cancer, certain medical tests, laboratory results, other illnesses, and past treatments received.

The eligibility criteria for each clinical trial have two sections: inclusion criteria and exclusion criteria. Inclusion criteria determine who may participate in the clinical trial. Exclusion criteria are conditions that determine if a patient may not be able to participate in a study. Both the inclusion and exclusion criteria are a vital part of the research plan to get credible and consistent results.

**Will insurance cover clinical trials?**

Tests and procedures that are considered standard of care (e.g., routine blood tests, X-rays, myeloma-specific measurements) are usually covered by health insurance policies. However, study-related tests and procedures are paid for by the study sponsor. These may include additional bone marrow biopsies, more frequent skeletal surveys, magnetic resonance imaging (MRI), positron emission tomography (PET), computerized axial tomography (CAT or CT), pharmacogenomics, pharmacodynamics, and pharmacokinetics-related tests.
How do I know that I am responding to the therapy in a clinical trial?

Remission or response
These terms are used interchangeably and refer to complete or partial disappearance of the signs and symptoms of cancer. Each trial is designed to assess response with predetermined tests that must be performed at the same laboratory to ensure uniform results.

Complete Response (CR)
CR is the absence of myeloma protein from the serum and/or urine by standard testing; absence of myeloma cells from the bone marrow and/or other areas of myeloma involvement; clinical remission and improvement of other laboratory parameters to normal. CR is not the same thing as a cure.

Very Good Partial Response (VGPR)
VGPR is just less than CR, that is, when myeloma protein levels are reduced by ≥ 90%, but not gone.

Partial Response (PR)
PR is a level of response less than CR. In SWOG studies, it has meant > 50% and < 75% response. In other studies it has meant ≥ 50% response.

Resources
There is much information available on the IMF website myeloma.org to help you find clinical trials, learn about recent clinical trial results, understand the current recommendations for optimal care of myeloma patients, and evaluate options when standard treatments are no longer working.

- The IMF's Myeloma Matrix 2.0: Smart Search is available at matrix.myeloma.org.
- If you are having trouble finding a drug you're looking for, remember that drug names change through the course of drug development. Drugs usually start out with a seemingly random set of numbers and letters, later acquire a generic name, and are given a brand name only if they are heading to approval.
- Filmed interviews with researchers who have presented important recent clinical trial data at the American Society of Hematology (ASH) and American Society of Clinical Oncology (ASCO) meetings are available on the IMF website at videos.myeloma.org.
- Patients considering clinical trials would do well to be familiar with the standards of care as set forth by the International Myeloma Working Group (IMWG). Their many publications are available at imwg.myeloma.org.

In closing
While a diagnosis of cancer is something you cannot control, gaining knowledge that will improve your interaction with your doctors and nurses is something you can control, and it will have a significant impact on how well you do throughout the disease course.

This booklet is not meant to replace the advice of your doctors and nurses who are best able to answer questions about your specific healthcare management plan. The IMF intends only to provide you with information that will guide you in discussions with your healthcare team. To help ensure effective treatment with good quality of life, you must play an active role in your own medical care.

We encourage you to visit myeloma.org for more information about myeloma and to contact the IMF InfoLine with your myeloma-related questions and concerns. The IMF InfoLine consistently provides callers with the most up-to-date and accurate information about myeloma in a caring and compassionate manner. IMF InfoLine specialists can be reached at InfoLine@myeloma.org or 818-487-7455 or 800-452-CURE.

Terms and definitions
Bone marrow biopsy: The removal, by a hollow-bore needle, of a sample of tissue from the bone. The cells are checked to see whether they are cancerous. If cancerous plasma cells are found, the pathologist estimates how much of the bone marrow is affected. Bone marrow biopsy is usually done at the same time as bone marrow aspiration.

Cancer: A term for diseases in which malignant cells divide without control. Cancer cells can invade nearby tissues and spread through the bloodstream and lymphatic system to other parts of the body.

Computerized axial tomography (CAT or CT) scan: A test using computer-ized x-rays to create three-dimensional images of organs and structures inside the body, used in myeloma to detect small areas of bone damage or soft tissue involvement.

Dose-limiting toxicity (DLT): Side effects severe enough to prevent giving more of the treatment.

Magnetic resonance imaging (MRI): A diagnostic imaging test that uses magnetic fields and radio waves, not ionizing radiation, to produce detailed two- or three-dimensional images of organs and structures inside the body. MRI gives very fine resolution of soft tissues, especially encroachments on the spinal cord, but is less accurate for bone lesions.

Maximum-tolerated dose (MTD): The highest dose of a treatment that most people can safely withstand.
**Multiple myeloma**: A cancer of the bone marrow plasma cells, white blood cells that make antibodies. The cancerous plasma cells are called myeloma cells.

**Overall survival (OS)**: The median number of individuals in a group who are alive after a particular duration of time. OS is often used as a measure of treatment efficacy in clinical trials. The lengthening duration of OS in myeloma trials makes it a difficult endpoint to use, leading to the effort to validate minimal residual disease status as a new endpoint.

**Performance status**: A measure of the level of activity of which a patient is capable. By implication, a measure of the severity of disease. Developed by the Eastern Cooperative Oncology Group (ECOG), the ECOG scale runs from 0 to 5, with 0 being “fully active, able to carry on all pre-disease activities without restriction,” and 5 being “death.” Also called ECOG status. Many clinical trials require ECOG status of 0 or 1; trials enrolling patients with a status of 3 or 4 are rare.

**Pharmacodynamics**: The study of the effect or effects of drugs on human cells.

**Pharmacogenetics** or **pharmacogenomics**: Interchangeable terms that refer to the study of specific changes in genes that result in various responses to treatments.

**Pharmacokinetics**: The study of the processes by which a drug is absorbed, distributed, metabolized, and eliminated by the body.

**Positron emission tomography (PET)**: A diagnostic test that uses a sophisticated camera and computer to produce images of the body. PET scans show the difference between healthy and abnormally functioning tissues based upon the uptake of radiolabeled sugar by active cancer cells.

**Progression-free survival (PFS)**: The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works. Also called PFS. See “Progressive disease.”

**Progressive disease**: Myeloma that is becoming worse or relapsing, as documented by tests. Defined as an increase of ≥ 25% from lowest confirmed response value in the myeloma protein level and/or new evidence of disease.

**Refractory**: Disease that is no longer responsive to standard treatments. Patients with refractory myeloma have had progressive disease either during treatment or within 60 days following treatment. Most clinical trials for advanced disease are for patients with relapsed and/or refractory myeloma.

**Skeletal survey (metastatic survey)**: A series of plain x-rays of the skull, spine, ribs, pelvis, and long bones to look for lytic lesions and/or osteoporosis.

**Stage**: The extent of a cancer in the body.

The IMF thanks the members of the Nurse Leadership Board (NLB) for their help in preparing this publication.