



**A Guide to  
Understanding  
Clinical Trials and  
Medical Research in**

**HEPATITIS C**

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# UNDERSTANDING CLINICAL TRIALS

## Definition and General Description of Clinical Trials

A clinical trial is a study designed to answer specific questions about a potential new therapy or new uses of an established therapy. The specific questions most often examined are about *safety*, i.e., what are the side effects or toxicity, and *efficacy*, i.e., does the drug work. A clinical trial may also be referred to as a research study.

Clinical trials are the best way to determine safety and efficacy. A clinical trial is conducted following a *protocol*, a set of procedures that are written in great detail, like a recipe. The protocol states how the clinical trial will be conducted, who can participate, how the drug will be administered, and how the participants will be followed. The protocol is reviewed by many people, including the sponsor of the study, the participating investigators, members of the local Institutional Review Board (IRB), and, in some circumstances, representatives of the Food and Drug Administration (FDA). This same general protocol is followed for study of an Investigational New Drug (IND) as well as for study of new uses of established drugs. If there are no objections, the trial can be initiated and testing can begin on human subjects.

## Clinical Trials for Chronic Hepatitis C

Hepatitis C is the most common blood-borne infection in the United States ([www.cdc.gov](http://www.cdc.gov)). An estimated 3.9 million Americans have been infected with hepatitis C virus (HCV) at some time in the past, and about 2.7 million have not recovered and have chronic infection. Although it is not certain how long HCV has been around, its existence became apparent in the 1970s when people with post-transfusion hepatitis tested negative for hepatitis A and B, which could be diagnosed using newly available tests. Unable to accurately identify the source of the infection, the term “non-A, non-B hepatitis” was coined in 1975. In 1989, after nearly 15 years of research, Michael Houghton and colleagues were able to isolate the virus, and non-A, non-B hepatitis was renamed hepatitis C.

The first test to precisely diagnose hepatitis C was based on detection of antibody to HCV (i.e., anti-HCV); the test became available in 1990. There are now newer generations of antibody tests that are more accurate. A later advance in the diagnosis of hepatitis C was the measurement of the

amount of the actual virus in the blood (serum HCV RNA, often called viral load) by polymerase chain reaction (PCR), branched chained DNA (bDNA), and more recently by transcription mediated amplification (TMA). The only approved virologic test as of 2001 is a PCR test.

Treatment for chronic HCV infection is a relatively new development. Therapy for chronic hepatitis C became available in 1991, with the FDA's approval of interferon alfa-2b, which is a genetically engineered synthetic interferon designed to mimic the body's natural interferon. Even though the exact mechanism of action of the alpha interferons is not completely understood, it is believed that one of their functions is to interfere with the production of new viruses, known as viral replication. In order to find treatments for chronic hepatitis C that are safe and effective, new drugs, including interferons, must undergo rigorous testing, including animal studies and clinical trials in humans.

## Clinical Trial Terminology

The language used in a clinical trial and the associated informed consent documents should be easily understandable to patients participating in the study. Knowing the meaning of commonly used terms is a valuable tool. In addition to the definitions provided in the glossary, it is especially important to know the meaning of the following terms:



**Hepatitis C  
is the most  
common blood-  
borne infection  
in the United  
States.**

- **Adverse event** – an undesired event occurring during the use of any drug.
- **Placebo** – a pill (or capsule, liquid, or injection) that contains an inactive substance. It is used in comparison to the experimental drug in *placebo-controlled* clinical trials.
- **Single-blinded or double-blind study** – this refers to whether or not the study participants and/or the research team knows whether the participants are receiving a placebo or the experimental drug. In a blinded study, the participants do not know if they are receiving the substance being tested or the placebo. In a double-blind study, neither the participants nor the researchers know who is receiving the experimental drug or the placebo. In the case of medical necessity, a study can be *unblinded* to reveal who is and is not receiving the experimental treatment.



After preliminary evidence of effectiveness is confirmed in phase II studies, expanded controlled and uncontrolled **Phase III** studies are conducted to gain additional information on effectiveness and safety. In this phase, the study drug is given to several hundred to several thousand of patients. In Phase III studies, the new drug may be compared to current standard therapy.

**Phase IV** trials are post-marketing studies conducted after the drug has been approved and marketed, often to further confirm safety. These studies are done in order to gain more specific information about the drug, such as how the drug interacts with other drugs or how it works in people with other diseases. Phase IV trials may include large numbers of patients (some Phase IV trials are small), and may reveal uncommon side effects that are too rare to show up in Phase II or III studies.

Laboratory testing is performed regularly while an experimental drug is being tested in humans, thus new information about the drug's safety and effectiveness comes from blood tests as well as patient interviews and physical examinations.

Before a drug is approved for marketing, it is called an *investigational new drug* (IND). The total time it takes to bring a drug to market can vary. The preclinical laboratory phase averages about five years, and the length of time an investigational drug is in clinical trials averages seven years. According to an article published by the FDA in 1999, only one in 1,000 compounds make it from the laboratory to human testing, and only one in five of these receive FDA approval for marketing ([www.fda.gov](http://www.fda.gov)).

## Enrollment Criteria

*Enrollment criteria* is the term used to describe the rules for defining who can participate in a clinical trial. Potential participants are chosen based on specific qualifications, and some will be excluded. Enrollment criteria include factors such as age, type of disease, current and past medical history, and medications. Factors that enable volunteers to qualify for the study are called *inclusion criteria*. *Exclusion criteria* are conditions that disqualify someone from participating. Some typical enrollment criteria for a HCV drug treatment trial might include:

- Age 18 years or older
- Serum HCV RNA positive
- Elevated serum ALT level
- Not currently receiving another study drug

- No other liver disease
- Not pregnant or breastfeeding
- Willingness to participate in the clinical trial
- Ability to give informed consent

## Informed Consent

In order to participate in a clinical trial, volunteers must understand what is involved, potential risks and benefits, and their rights. The clinical trial should be explained in sufficient detail to address these issues. Before agreeing to enroll in a study, an interested person is given a document that describes the clinical trial and the rights of the participants. This is called an informed consent document. The prospective participant should have adequate time to read the consent form. The consent form can be taken home and discussed with family and friends or with a physician, such as a family doctor or referral doctor. It may be helpful to write down questions about any information that is unclear. The goal of the informed consent process is to ensure that the volunteer is completely informed about the potential risks and benefits before agreeing to participate in the study. Participants must also be informed of their rights (see next section).

Although the consent form is a written document, the consent process also involves discussion between the prospective volunteer and the research team. The participant's questions should be fully answered. The person obtaining consent should be certain that the volunteer understands the risks and the responsibilities associated with participation in the study. The volunteer should be aware of other treatment and/or non-drug alternatives if he or she does not enroll in the study. A signed and dated copy of the consent form should be given to the participant.

The consent form should include the following:

- Adequate information about the study in language the reader is able to understand
- The name of the investigational drug being studied
- What the researchers hope to accomplish
- What will actually be done in the trial
- The length of the study
- Identification of all diagnostic tests that will be performed related to the clinical trial
- Potential benefits and the risks, including known side effects of the drug

**Although the consent form is a written document, the consent process also involves discussion between the prospective volunteer and the research team.**

- What alternative treatments are available
- The name of the sponsor of the study
- Discussion of financial issues affecting the study participant
- The financial issues involved in the clinical trial, such as any costs the subject may incur
- How to contact the IRB and the Principal Investigator of the study
- Instructions on what to do if the subject believes there has been a research-related injury
- Discussion of the issue of participating in more than one clinical trial at the same time

An informed consent document does not waive any of the participant's legal or medical rights. The research team remains liable for any damage due to negligence. Volunteers do not waive their right to privacy. However, the FDA and others associated with the conduct of the trial may examine or copy participants' medical records. When possible, subjects' identities are kept confidential. The identities of participants are never published.

The consent form should state that participants can withdraw or that the study might be stopped at any time. It should mention if any of the researchers are receiving funding or financial gain as a result of conducting the study. The consent form should also state that no guarantees of benefits can be made.

If new information is learned about the drug, a subject's condition, or the study in general, the participant must be told. Occasionally the emergence of new information during the course of the study may require the consent form to be revised. If this occurs, the participant will be asked to sign another consent document. The goal is to keep subjects apprised of any new information that might influence their willingness to continue in the study. Informed consent is an ongoing process that continues throughout the clinical trial.

In addition to the federal requirements for the consent process, some states have their own requirements. An example of one state's requirements can be found in the appendix.

## Protecting the Rights of Participants

The rules and regulations for clinical trials are elaborate and well designed. Safety and the rights of participants are strongly protected. Before a trial can begin, it must meet the strict set of standards required by the FDA. Additionally,

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• **In addition to  
FDA and IRB  
rules, there  
are local,  
national and  
international  
regulations that  
dictate ethical  
conduct in  
research.**  
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an IRB must approve every trial before human subjects can be enrolled. An IRB is a multidisciplinary group that includes doctors, scientists, pharmacists, and non-scientist community representatives; the IRB may also include psychiatrists, attorneys, nurses, and other professionals. Clinical trials are reviewed throughout the course of the study, and all people associated with the trial are required to keep records long after the study has terminated. Participants must be informed of their rights, including the right to drop out of a study for any reason without influencing their subsequent medical care.

All clinical research must be conducted in an ethical manner. In addition to FDA and IRB rules, there are local, national and international regulations that dictate ethical conduct in research. Some well-known examples are the Nuremberg Code, the International Code of Medical Ethics, the Declaration of Helsinki, and the Belmont Report. These codes set forth some basic principles ([www.fda.gov](http://www.fda.gov)). These principles are: 1) the main purpose of research is to improve and advance medical science; 2) the physician's utmost priority is the health of the patient; and 3) risks should be minimized and should be outweighed by potential benefits.

The following are some of the rights of subjects who participate in a clinical trial:

- All persons who participate in a clinical trial must be willing volunteers.
- Subjects may not be coerced, misled, or unfairly induced into participating in a clinical trial.
- Participants are free to leave the study at any time, and are not required to give an explanation.
- The standard of medical care should be the same whether or not a patient chooses to participate in a clinical trial; the same is true for subjects who drop out of a trial.

## **Women of Childbearing Potential and their Sexual Partners**

Clinical trials of new drugs almost always exclude women who are pregnant or breastfeeding. Sometimes the sexual partners of women who are pregnant or breastfeeding are also excluded. Women of childbearing potential are no longer routinely excluded from clinical trials. However, women of childbearing age who could potentially become pregnant are required to use one or more effective forms of contraception. This requirement may also extend to the female partners of male participants in a trial. Women who are post-menopausal or who have had a total hysterectomy

are not considered to be of childbearing potential. Subjects and/or their partners who have had a tubal ligation or a vasectomy are *not* considered to be 100% protected against pregnancy.

## Clinical Trial Sponsors

The cost of conducting a clinical trial is enormous. Funding for a trial can come from various sources. Pharmaceutical companies sponsor the majority of clinical trials. In addition, the U.S. federal government provides funding through the National Institutes of Health. Investigators may also receive research money from public, industry and other private grants.

Part of the informed consent process includes disclosure of the funding source for the research. If a private company finances a clinical trial, the FDA requires all of the investigators who are associated with the trial to file a financial disclosure statement. This is a statement that gives details of the investigator's financial relationship with the sponsor. It states whether there is any possible conflict of interest between the ethical conduct of the study versus potential financial gain. Indirectly, this document reminds researchers that if they retain a significant financial interest in a company, they should examine their involvement in the study.

## Complaints about Trials

The informed consent document should provide the names and telephone numbers of persons to contact if there are complaints about any aspect of the clinical trial. Usually this is the Principle Investigator or research coordinator. The phone number of the IRB should also be listed on the consent form. If the complaint is still unresolved after contacting the investigator and the IRB, the next step is to contact the FDA or the U.S. government's Office for Human Research Protection (OHRP). See the resource section for contact information for these agencies.

# CONSIDERATIONS BEFORE ENTERING A CLINICAL TRIAL

## Questions to Ask

Since clinical trials vary, below are some questions to ask when considering participation:

- What is the purpose of the study?
- What is the drug or combination of drugs being tested?
- What is the study phase? If the trial is in an early phase, how many humans have received the study drug? What is known about animal studies using this drug?
- Is a placebo being used? If so, what are the chances of receiving the study drug versus the placebo? If I receive the placebo, will I be offered the study drug at the end of the trial period?
- If this is a double-blind placebo study, when can I expect to know if I received the placebo or the study drug?
- What side effects can I expect from the study drug? Are there any serious risks? If I were harmed as a result of the research, what treatment would I be entitled to receive?
- What are the potential benefits or risks of my participation in the study?
- What other treatment or non-drug options are open to me if I do not participate in the study?
- Will I receive lab tests or other diagnostic tests throughout the study? If so, how often? Will I be told the results during the study or will the results be revealed after the end of the trial?
- What is the duration of the clinical trial? What is the schedule of visits? Are there any other expectations that will require my time and effort?
- Where is the study being conducted?
- What should I tell my family or coworkers regarding my participation in the trial?
- Will I continue to see my regular physician if I participate in the study?
- Will I incur any costs? Will any of the treatment or tests be free?
- How many subjects will participate in the study?
- Will I be able to continue taking my regular medications or supplements (including prescription and over-the-counter medications, vitamins, minerals, and herbs)?

**Ultimately it is up to the potential participant to decide whether to take part in the clinical trial.**

## Risk versus Benefit

When considering a clinical trial, it is important to consider the relationship between the potential risks and benefits, called the *risk/benefit ratio*. The IRB requires an analysis of the risk/benefit ratio in order to determine if the possible benefits outweigh the possible risks. However, ultimately it is up to the potential participant to decide whether to take part in the clinical trial. Comparing possible risks and benefits is an essential part of this decision.

The following are some standard possible risks and benefits:

### ***Potential risks:***

- The possibility of not receiving the new study drug
- The possibility that the treatment will not be effective
- The risks of foreseeable and unforeseen adverse reactions or side effects
- The extra time involved in appointments and record-keeping

### ***Potential Benefits:***

- Possibility of free medication
- Possibility of free or less expensive care (this is not always offered)
- The possibility of receiving early access to a possibly effective treatment (this is not guaranteed)
- More time spent with the healthcare team, including close monitoring and follow-up

## Finding Clinical Trials

The following are some resources for locating clinical trials:

- Ask your doctor
- Contact the largest, most reputable medical centers in your area
- Consult local support groups
- Consult publications, both professional and patient-oriented
- Conduct research on the Internet
- Use e-mail and online discussion groups
- See the resource section of this publication

## Types of Studies

Every day, physicians make many patient-management decisions. Each decision involves weighing benefits and risks and determining the course of action judged to be in a patient's best interest. In making these decisions, physicians depend upon the medical literature as well as their experience and intuitive integration of the literature as it applies to specific patients. In general, there is a move to practice what has come to be called *evidenced-based medicine*, based on the synthesis of medical literature as it relates to a specific patient's condition.

Treatment decisions are often based on the strength of the medical literature specific to a particular disease or condition. The scientific strength and validity of published information on the treatment of a specific condition with a particular drug may vary considerably. *Clinical observations*, also known as *anecdotal evidence or case studies*, are the collection of information based on clinicians' observations. A *case study* of one or only a few patients does not receive much weight, because the total number of patients is too small to obtain statistically significant results, and there may be bias in the selection of patients reported. *Physiologic studies*, which measure some bodily function related indirectly to the effectiveness of a therapy, are often correct within the context of the physiologic study, but may be wrong when applied more broadly.

The most reliable research results come from a *prospective study* carefully planned and conducted in a standard manner with well-defined patient populations and treatment protocols. The larger the number of participants, called the *sample size*, the more valid are the results. Prospective studies are more reliable when subjects do not know if they are receiving the study drug or a placebo (a *blind study*), and most reliable when neither the subjects nor the investigators know whether the study drug or placebo is being administered (a *double-blind study*). Knowledge that a new drug is being given might subjectively influence, in a positive manner, the recording of treatment endpoints, while knowledge that a placebo is being taken might negatively influence the collection of information on the drug's effects.

When studies are completed, the results are often presented informally at meetings arranged by a sponsor, or manufacturer, of a drug. In addition, preliminary study

conclusions and some of the data may be presented at medical meetings and published as an *abstract* (a very brief synopsis of the study). The most comprehensive information comes from research articles published in medical journals after peer-review. Peer-review means that the paper is reviewed by two or three independent physicians or investigators with no relationship to the study authors or sponsors. In addition, the editor and associate editors of the journal also carefully review the research study methods and conclusions. These *peer-reviewed studies*, when published in a prestigious journal, carry great weight. The FDA also reviews every piece of the original data from the clinical trial in detail before approving a new drug for use. Every single patient record is scrutinized to confirm the accuracy of the data and the statistical analysis.

Determining if the results of a study are valid may be challenging. For example, if a treatment was studied predominantly in middle-aged men, will it also be safe and effective for a woman over age 65? Studies of new drugs usually involve a population of similar people (homogeneous population). However, even a study that uses a homogenous population needs to be examined in a critical manner. For instance, what does it mean when a response rate of 40% to an HCV therapy is reported? Does this response rate apply to patients with all HCV genotypes? The results of therapies for HCV infection may be different for each genotype.

Do the final numbers include all of the participants in the study, or only the ones who stayed in the study for its entire length? If a study analysis includes all of the data from all of the participants based in accordance with the study arm in which they were originally enrolled, it is an *intent-to-treat* analysis. How many subjects dropped out of the study because of side effects? If a study analysis excludes participants who dropped out early due to side effects or for some other reason, it is an *as-treated* analysis. In addition, will the new drug be safe and effective for a person with other medical conditions such as mild depression and mild heart disease? This type of question may be answered in Phase IV studies, which monitor safety and effectiveness after a new drug is marketed and more widely used.

Another concern in randomized controlled trials — in which study participants are similar and receive either an experimental drug, or a standard treatment or a placebo —

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- **The larger the**
- **number of**
- **participants,**
- **called the**
- **sample size, the**
- **more valid the**
- **results are likely**
- **to be from a**
- **statistical**
- **standpoint.**
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is the validity of the tests or observations used to assess *endpoints* of treatment. The sensitivity or accuracy of a test is also important. Some of the serum HCV RNA tests may not detect low levels of the virus in the blood. Finally, whatever test is used must be clinically relevant to the patient and the specific disease or condition.

## Understanding Statistics

Most studies have historically used the p-value to indicate whether the results of a study are significant, or clinically important. In other words, what is the chance that treatment with a new drug has no effect (the so-called *null hypothesis*) versus the chance that it has a positive effect? Based on tradition, a p-value of  $< 0.05$  is used as the determination of *statistical significance*, or a positive result. What this means in a general sense is that a p-value of  $< 0.05$  indicates that there is a 95% chance that the drug really works (true positive) and only a 5% chance that it does not (false positive). A p-value of  $< 0.01$  is considered “highly significant.”

Finally,  
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is used must  
be clinically  
relevant to  
the patient  
and the  
specific  
disease or  
condition.

The proper use of statistics is more complicated than the above explanation. Some studies involve thousands of patients, while others involve relatively few patients. A *false positive* error (also called type I, or  $\alpha$  error) using  $p < 0.05$  means that the drug may not really work AND is greater in smaller studies. Studies with more participants are said to have a higher *power*. Studies must be large enough to avoid concluding that the effectiveness of a new treatment is the same as that of the standard treatment or placebo (i.e., a *false negative* result, also called a type II, or  $\beta$  error) when it is in reality better. What if the results of a study of a new versus the standard drug are deemed negative because it results in a p-value of, for example, 0.1 or 0.06? This is just above the arbitrary 0.05 level, below which studies are considered significant by convention. Is this truly a negative result? More sophisticated statistical analysis (using a technique called *confidence limits* or *intervals*), or repeated and larger studies, can sometimes help determine the “truth” about a new drug.

## A Final Word

It takes years of education and experience to become an expert in the field of research. The purpose of this guide is to provide tools to assist those who are interested in learning more about clinical research and HCV. A curious mind coupled with time and practice can open the doors to knowledge. And as the saying goes, knowledge is power.

## The Internet as a Source

The Internet can be a valuable tool. However, like any tool, one needs to know how to use it well. The following are some suggestions for how to use the Internet more effectively:

- Find out if the information comes from a reliable source. Information from independent and not-for-profit sources, particularly from the U.S. federal government (e.g., National Institutes of Health, FDA), a general medical society (e.g., American Medical Association) or specialty or disease society (e.g., American Association for the Study of Liver Diseases) is likely to be reliable. Commercial sources (e.g., pharmaceutical companies) may be scientifically accurate, but may emphasize the positive aspects of a drug for marketing purposes.
- Look for information that includes author names, medical affiliations, references, and when the material was written.
- Information provided in chat rooms and discussion forums is often anecdotal and based on individual experiences, which often cannot be generalized to all people with the same condition, such as chronic hepatitis C.
- Get a reliable second opinion to confirm your understanding of the research.
- Question what you read. Does the research stand up to careful scrutiny?
- Don't panic. It is easy to be overwhelmed and frightened by what appears to be "bad news." Get more information before overreacting.
- Never use the Internet as a substitute for medical care.

## Information Sources

- Center for Drug Evaluation and Research  
[www.fda.gov/cder](http://www.fda.gov/cder)
- CenterWatch  
[www.centerwatch.com](http://www.centerwatch.com)
- NIH Clinical Trials  
[www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- Food and Drug Administration (FDA)  
[www.fda.gov](http://www.fda.gov)

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• **Never use the  
Internet as a  
substitute for  
medical care.**  
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- Hepatitis C Support Project  
[www.hcvadvocate.org](http://www.hcvadvocate.org)
- Medline Plus  
[www.nlm.nih.gov/medlineplus](http://www.nlm.nih.gov/medlineplus)
- National Library of Medicine  
[www.ncbi.nlm.nih.gov/PubMed](http://www.ncbi.nlm.nih.gov/PubMed)
- Office for Human Research Protection (OHRP)  
<http://ohrp.osophs.dhhs.gov>
- National Institutes of Health (NIH)  
[www.nih.gov](http://www.nih.gov)
- Stanford University Medical Center  
<http://clinicaltrials.stanford.edu>

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# GLOSSARY



## **Adverse event**

an undesired action or effect of an experimental treatment.



## **Alpha interferon**

a naturally occurring protein in the human body produced by the immune system. Interferon interferes with viral replication. Genetically engineered products based on the natural protein have been developed by several pharmaceutical companies, and are approved for the treatment of chronic HCV infection.



## **ALT**

abbreviation for alanine aminotransferase. ALT is an enzyme produced inside liver cells and is frequently elevated in people with chronic HCV infection because of minor breakdown of the membranes of liver cells due to inflammation. Serum ALT levels are measured in a common blood test.



## **Antibody**

a protein produced by the immune system when a foreign substance enters the body. The presence of antibodies is an indicator of a past or possibly current infection. HCV antibodies are written as *anti-HCV*. The test for anti-HCV is often the first step in diagnosing chronic HCV infection. A positive anti-HCV test must be followed by other laboratory tests in order to confirm the diagnosis. The antibody test alone is not sufficient to make a diagnosis of chronic HCV infection.



## **Biochemical response**

how a person's patient's serum ALT responds to treatment. When a patient's elevated serum ALT level becomes normal after HCV therapy has been initiated, this is considered a biochemical response.



## **Biopsy**

a procedure in which a sample of cells or tissue is taken to examine in a laboratory. In HCV, liver biopsies are used to monitor the health of the liver.



## **Blind or double-blind study**

this refers to whether or not the study participants and/or the research team knows whether the participants are receiving a placebo or the experimental drug. In a blinded study, the participants do not know if they are receiving the active new drug or the placebo. In a double-blind study, neither the participants nor the researchers who administer the treatment know who is receiving the experimental drug

or the placebo. In the case of medical necessity, a study can be *unblinded* to reveal who is and is not receiving the experimental treatment.

• • • • • • • • • • **Combination therapy**

two or more drugs that are used in combination with each other in order to improve the effectiveness of treatment. When applied to HCV treatment, this term most often refers to the use of interferon plus ribavirin.

• • • • • • • • • • **Control group**

the group of participants in a clinical trial who receive the current standard treatment or no active treatment, and not the new drug under study.

• • • • • • • • • • **Exclusion criteria**

conditions that disqualify someone from participating in a clinical trial.

• • • • • • • • • • **Experimental group**

the group of study participants who receive the new experimental treatment.

• • • • • • • • • • **FDA**

abbreviation for the Food and Drug Administration. This U.S. federal government agency has many functions. It is responsible for granting or denying approval for drugs to be sold to the public.

• • • • • • • • • • **Genotype**

genetic variation in the structure of HCV, resulting in six major genotypes, designated by the numbers 1 through 6. There are also many subtypes, e.g., 1a, 1b, 2a, etc. In the U.S., genotype 1 is predominant (approximately 70-75% of patients).

• • • • • • • • • • **HCV RNA**

the genetic material of the hepatitis C virus. HCV is a single-stranded ribonucleic acid (RNA) virus.

• • • • • • • • • • **Half-life**

The period of time it takes for the concentration of a drug to decrease to half its original concentration in the blood.

• • • • • • • • • • **Histological**

refers to bodily tissue. In HCV, it is applied to liver tissue. *Histological improvement* means improvement in liver tissue, either reduced inflammation or reduced fibrosis, when comparing pretreatment biopsies with biopsies obtained typically six months after HCV therapy.

- • • • • • • • • • • **Inclusion criteria**  
conditions that must be met in order to be eligible for a clinical trial.
- • • • • • • • • • • **Institutional Review Board (IRB)**  
an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. It has the authority to approve, require modifications in, or disapprove research. The purpose of IRB review is to protect the rights and welfare of humans participating in research.
- • • • • • • • • • • **Investigational new drug (IND)**  
a drug that the FDA allows to be used in human clinical trials in order to gain information for evaluation by the FDA, usually for approval of commercial marketing.
- • • • • • • • • • • **Investigator**  
a clinical researcher who is involved with a clinical trial protocol and its implementation. The *Principal Investigator* is ultimately responsible for the conduct of the trial.
- • • • • • • • • • • **Monotherapy**  
use of a single drug for treatment. Traditionally, monotherapy for chronic HCV infection is interferon alone.
- • • • • • • • • • • **Nonresponder**  
a person who does not show sufficient improvement while undergoing treatment. In HCV, a nonresponder is person who does not experience a normalization of ALT levels or disappearance of HCV RNA.
- • • • • • • • • • • **Placebo**  
a pill (or capsule, liquid, or injection) that contains an inactive substance. It is used in comparison to the experimental drug in *placebo-controlled* clinical trials.
- • • • • • • • • • • **Protocol**  
a written document that states the guidelines of how a clinical trial will be conducted. A protocol includes all of the details of the study, including who can participate, how the study drug will be administered, drug side effects, and risks.
- • • • • • • • • • • **Randomization**  
The process of randomly assigning study participants to either the control (standard treatment or no treatment) or experimental (new drug) group.
- • • • • • • • • • • **Response to treatment**  
how a disease responds to drug therapy. The term can refer to a biological, histological, or virological response.

- • • • • **Responder-relapser (or relapser)**  
a person who initially responds well to a treatment but then experiences a relapse. In chronic HCV infection, this is someone who initially has a positive response to treatment (normal ALT and loss of HCV RNA), but does not sustain that response when therapy was stopped.
- • • • • **Ribavirin**  
an antiviral medication that is used in combination with an interferon product for treatment of chronic HCV infection.
- • • • • **Risk/benefit ratio**  
a measurement used to evaluate whether potential benefits outweigh potential risks.
- • • • • **Standard treatment**  
the best or most widely used currently available treatment.
- • • • • **Study arm**  
clinical trials usually compare the responses of two or more groups of subjects (e.g., control and treatment groups). If a study has more than one treatment group (for example, receiving varying dosages of a drug), the different groups are called study arms.
- • • • • **Sponsor**  
the sponsor of new drug studies is typically a drug or biologic manufacturer. Other potential sponsors include a university or independent foundation supporting the research.
- • • • • **Subject**  
a volunteer participant in a clinical trial.
- • • • • **Sustained responder**  
a person who maintains a long-term response to treatment. In HCV, a sustained responder has a long-term beneficial result from HCV treatment (usual endpoints are normal ALT and negative HCV RNA) that persists after treatment has been stopped (six months is the generally accepted time interval after stopping treatment that defines a sustained response and that correlates with a long-term benefit)
- • • • • **Treatment-naive**  
a person who has not had prior treatment for a particular condition.
- • • • • **Viral load**  
the amount of virus (i.e., the HCV RNA level) that can be measured, usually in the blood.

..... • **Viral replication**  
the ability of a virus to reproduce copies of itself.

..... • **Virological response**  
how a person's viral load level responds to treatment. In HCV, when a patient's HCV RNA becomes undetectable after HCV therapy has been initiated, this is considered a virological response. If the HCV RNA remains negative beyond six months, the term *sustained virological response* is used.

..... • **Virus**  
a microscopic infectious particle that invades a living organism and makes copies of itself (viral replication).



## Informed Consent

The following is an example of the list of patients' rights that must be included in informed consent documents in the state of California:

As a human subject you have the following rights. These rights include, but are not limited to, the subject's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, and their relative risks and benefits;
- be informed of the avenues of medical treatment available, if any, to the subject after the experiment if complications should rise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time, and that the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form;
- and be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.



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