



Making Sense of



**Research and
Medical Literature**

Lucinda K. Porter, RN

A publication of the Hepatitis C Support Project



HCV ADVOCATE
www.hcvadvocate.org



This information, provided by the Hepatitis C Support Project, is not medical advice. The mission of the Hepatitis C Support Project is to offer support to those affected by chronic hepatitis C virus infection (HCV), hepatitis B (HBV), and HIV/HCV coinfection. Support is provided broadly, through information and education, as well as access to support groups. The Project seeks to serve the HCV community as well as the general public.

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HEPATITIS C

● *Foreword*

A newspaper headline states, “*New Treatment Discovered for Hepatitis C.*” An Internet site claims “*more patients responded to drug A than drug B.*” Your doctor prescribes a new medication for you and there are nearly 50 side effects listed for it. You attend a hepatitis C conference and each drug company tells you why their drug is better – all backed by research.

How do you know what is true? More specifically, what is true *for you*? If you do not have a research background, it may be difficult to understand statistics or scientific language. However, research is a bridge between disease and health. Your ability to cross that bridge may affect your future.

As you learn to live with HCV, you will make numerous decisions. These will include lifestyle, HCV management, and treatment choices. Your medical providers will advise you, but in the end, you decide what is right for you. Informed decisions likely lead to better outcomes.

How does someone living with HCV become informed? It takes education, curiosity, and patience. There are simple tools to help you wade through even the most complicated research. The purpose of this guide is to educate. The fact that you are reading this shows that you have curiosity. Add in some patience and the rest will fall into place. This guide will not turn you into an HCV expert. However, it will help you strengthen your skills in the area you are already an expert in – your own health.



Lucinda K. Porter, RN
Author of *Free from Hepatitis C*
and *Hepatitis C Treatment One
Step at a Time* and a long-time
contributor to the *HCV Advocate*

HEPATITIS C

Hepatitis C is the most common blood-borne virus in the United States (www.cdc.gov). More than 4 million Americans have been infected with the hepatitis C virus (HCV) at some time in the past, and about 2.7 to 3.9 million have not recovered and have chronic infection.

Although HCV has been around a long time, knowledge about it is relatively new. Before it was accurately identified, it was called *non-A, non-B hepatitis*. In 1989, Michael Houghton and colleagues were able to isolate the virus, and non-A, non-B hepatitis was renamed hepatitis C.

Treatment for chronic HCV infection is a fairly new development. Therapy for chronic hepatitis C became available in 1991, with the Food and Drug Administration's (FDA) approval of *interferon-alfa*. This is a genetically engineered synthetic interferon designed to mimic the body's natural interferon. Another advance in HCV treatment occurred in the late 1990's with the addition of ribavirin (RBV) to interferon. Although not fully understood, ribavirin weakens HCV, making it harder to multiply. A significant HCV treatment advance occurred in 2001 with the approval of *pegylated* interferon (PEG). Pegylation is a process that stabilizes the interferon, making it more effective.

Now there are HCV direct-acting antiviral (DAAs) medications with and without ribavirin that can cure up to 90% to 100% of most people with hepatitis C who take the medications.

These medical advances are only the beginning. Our understanding of HCV, and how to treat it, is growing rapidly. New therapies and variations using existing medications have raised the level of hope for the future for millions of people worldwide.

Evidence-based medicine is the practice of using solid research in order to formulate treatment recommendations.

CLINICAL RESEARCH

Every day, medical providers 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. Providers use their clinical expertise along with medical literature to guide these decisions. An important question is, *upon what evidence is a treatment recommendation made?* This is *evidence-based medicine*. The best evidence comes from solid, rigorously reviewed research.

Scientific study tries to answer questions about how to treat a disease. Clinical research, research studies, and clinical trials are similar terms that describe the procedure to answer these questions. A trial is a study designed to answer specific questions about a potential new therapy or new uses of an established therapy, as in "off-label" use. The specific questions most often examined are about *safety* and *efficacy*. *Safety* refers to the drug's toxicity or side effects. *Efficacy* refers to the drug's effectiveness, i.e., if it works.

Drug research usually tests laboratory animals before humans. Laboratory animals are protected by strict regulations.

Clinical trials follow 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 monitored. 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)*. A protocol is required whether the study is for new drugs or for new uses of drugs that are already FDA-approved. The trial cannot begin until everyone approves the design.

Although heavily regulated, clinical trials are not necessarily good for all patients. Protocols vary in quality, objectives, and level of risk. To judge whether a clinical trial is appropriate for you, you need to examine it closely. This guide will suggest ways to do this.

● *Phases of Clinical Trials*

In order to find treatments for chronic hepatitis C that are safe and effective, new drugs, including interferons, must undergo rigorous testing. Drug research involves many stages. Much of the knowledge about drugs is derived from initial laboratory research in animals. Animals are used during the drug development phase, primarily to confirm lack of toxicity. If laboratory tests show that a drug has potential therapeutic value without major toxicity, it may advance to the next stage. The next step involves an extensive process of applying to the FDA for permission to proceed. After careful review of the preliminary data, if the FDA gives its approval, then drug testing – clinical trials – can begin on humans.

Clinical trials may have up to four phases. The initial introduction of an investigational new drug using humans occurs in **Phase I**. The subjects in this phase are usually healthy volunteers (usually 20 to 80 subjects). Sometimes the subjects are those with the disease that is being studied. The goals of a Phase I trial are to evaluate safety and tolerability (i.e., lack of major side effects) as well as the dosage range. This is determined by testing a range of doses (called a *dose-ranging* trial). Study participants initially receive a low dose of the drug; this is gradually increased as long as the drug appears to be safe. Phase I studies may provide early indications of the drug's effectiveness, but whether or not a drug works is the primary focus of Phase II and Phase III studies.

In **Phase II** trials, clinical studies are conducted using patients with the disease for which the drug is being tested. The goal of this phase is to obtain preliminary data on the effectiveness (also known as *efficacy*) of the test drug. This phase also allows further collection of data on the common short-term side effects and risks associated with the drug. A relatively small number of participants enroll in Phase II studies (100 to 300 subjects).

After confirming preliminary evidence of effectiveness in Phase II studies, the goal of **Phase III** studies is to gain additional information on effectiveness and safety. In this phase, several hundred to several thousand subjects receive the test drug. In Phase III studies, the new drug is often compared to current standard therapy.

After the drug is approved and marketed, the FDA may require a company to obtain more information about the drug. These studies occur as **Phase IV** trials. Examples are the safety and efficacy of varying doses,

how the drug interacts with other drugs, or how it works in people with other diseases. Phase IV trials may include small or large numbers of subjects and may reveal uncommon side effects that are too rare to show up in Phase II or III studies.

● *Drug Development: Timeline and Cost*

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. According to the FDA, the preclinical laboratory phase ranges from 1 to 3 years with an average of 18 months. The length of time an investigational drug is in clinical trials ranges from 2 – 10 years, averaging 5 years. The FDA review and approval process may take up to 7 years, while averaging 2 years. The average total time from bench to market is almost 9 years. According to the FDA, only one in 1,000 compounds makes it from the laboratory to human testing, and only one in five of these receives FDA approval for marketing (www.fda.gov).

The cost of conducting a clinical trial is enormous. A price tag of several hundred million dollars is common. The total price from the lab to the pharmacy may be over a billion dollars. Funding for a trial can come from various sources, with the majority sponsored by pharmaceutical companies. In addition, the U.S. federal government provides funding through the National Institutes of Health. Investigators may also receive research money from the public, from industry and from other private sources.

● *Types of Studies*

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 carry 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.

The most reliable research results come from a *prospective study*. Simply put, prospective studies look ahead with the intention of collecting data. These studies are carefully planned and conducted in a standard manner with well-defined patient populations and treatment protocols. The number of participants is known as the *sample size*. The larger the sample size, the more valid the results.

Prospective studies are more reliable when subjects do not know if they are receiving the study drug or a *placebo* (an inactive substance). This is called a *blind* study. The most reliable condition is when neither the subjects nor the investigators know whether the study drug or placebo is being administered (a *double-blind* study). Although researchers and patients try to remain objective, they may unknowingly influence the results. For instance, if a nurse knew you were on a study drug, he or she might unintentionally treat you differently than if it was thought you were on the placebo. As a patient, you might act differently if you thought you were receiving a placebo.

Retrospective studies look at past data. Retrospective studies are used to gain understanding for situations that have already happened. If someone wanted to know what the risk factors were for people with HCV, they would conduct a retrospective study. Retrospective studies are great for gaining understanding but they are not prospective studies since the outcome is already known. Even the best scientists can be biased, so most drug studies are prospective and double-blinded.

If a particular topic interests you, look at an article's reference section to find more articles on that subject.

Head-to-head clinical trials compare two or more drugs or treatments. These studies are good ways to compare medications to see if one is more effective. A true head-to-head trial maintains identical factors except for the one variable you are studying. Unfortunately, even the most carefully designed studies may be flawed, particularly if the researcher favors one of the drugs.

Medical literature and research articles can be hard to understand. Be patient – with practice it will get easier.

HOW TO READ MEDICAL RESEARCH ARTICLES

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.

When learning how to read medical literature, start with peer-reviewed articles in well-known medical publications, such as *Hepatology*, the *American Journal of Medicine* or the *New England Journal of Medicine*. When published in prestigious journals, these peer-reviewed studies carry great weight.

**It may be helpful to have a medical dictionary at hand.
The Internet is a good place to find definitions.**

Journal articles follow similar formats. Most articles start with an *abstract*. This is a brief summary of important points of the research article. The larger article begins with an *Introduction* or *Background*. This is followed by the *Methods* section, the *Results* or *Findings* section and the *Discussion* or *Findings* section. *References* are listed at the end.

Read with a critical mind. Before you begin, formulate some questions that you want answered. What are you looking for? Does the research discuss people who are similar to you? For instance, if you are 65 years old and everyone in the study was under 40, then perhaps the research does not apply to you. In short, look at what was studied, who was studied, how they were studied, and what the conclusions were.

First, read the abstract. The abstract may tell you if the article applies to you. If only men were studied, women may want to look for studies that included both sexes. The abstract is a quick way to decide if you want to read the rest of the article.

! *When reading a medical article, ask: What was studied? Who was studied?
● How were they studied? What were the conclusions?*

The *introduction* or *background* section describes what is known and unknown about the topic. Every fact in this section comes from another source. This is known as a *citation*. If you want to know where the citation came from, look for a number or name alongside the text. This will match a name or number in the *reference* section listing the source of the information.

The *methods* section describes the design of the study. It tells you who and what was studied, how it was done, and how the results were evaluated. Here are important points to explore:

- a. How many subjects were enrolled in the study? Larger studies carry more weight.
- b. Who participated in the research and how were they chosen? Were they evenly matched by age, gender, race, genotype, weight, viral load, degree of liver damage, general health and other important variables?
- c. Was the clinical trial *randomized* and blinded to prevent bias? (Subjects are selected randomly to a particular study group to receive the test drug, a standard of care drug or a placebo.) The double-blind, randomized control trial is the most desirable design.
- d. What kind of study was it, i.e., prospective, retrospective?
- d. How did the researchers test their theory and what tools did they use? Were they using sensitive diagnostic tools?
- e. Was the study designed to compare one drug against another drug, or against the current standard of care? Was the dose of medication appropriate in both groups? Was there only one variable or were there many?

The *results* or *findings* section reports on the outcome of the study. It should break down the information by overall results and then by patient characteristics and medication dose. The results should also report the statistical significance – an indicator of how well the drug will work under the same circumstances in a different setting. This is usually reported as a *p-value*. A *p-value* of < 0.05 (less than 5%) is considered statistically significant. $P=0.05$ means that there is a 95% chance the drug will work and a 5% chance that it will not.

Research articles end with some sort of conclusion, summary, or recommendation. This is the bottom line. The author(s) state what they found and what they did not find. The strengths and weaknesses of the trial may be discussed. Not coming to a conclusion is just as important as coming to one. The conclusion should be consistent with the results.

If you are short on time, you may be tempted to read only the conclusion. This is fine if the research is good and applies to you. However, it is best to read the entire article – even if you do not understand it. The more you practice reading medical literature, the more you will be able to understand the information presented. Use a critical mind when trying to interpret scientific data or any other source of information. Do not be afraid to ask questions – most medical professionals welcome questions and the involvement of patients in their medical care and management.

● *Making Sense of Medical Literature*

Reading medical literature is only a small part of educating yourself. Making sense of what you read is the important part. To do this, you need to apply *critical thinking*. Critical thinking is a process of gathering information, analyzing it and evaluating it.

Critical thinkers try to determine if information is fact. They look closely at research results to see if they are valid. 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 who were originally enrolled, it is an *intent-to-treat* analysis. However, 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*.



Don't believe everything you read. Learn to be a critical thinker.

Example: Study #1 uses an intent-to-treat analysis. The final report states that 50% of the participants were cured. Looking at the data, you noticed that 100 people enrolled in the study. 25 people dropped out because of side effects; another 25 were not cured. The remaining 50 participants were cured, which equals 50%.

Study #2 claimed their drug was better because they had a 67% cure rate. However, this study used an as-treated analysis. They also started with 100 participants and had 25 drop out because of side effects. However, they analyzed the data based on the remaining participants. By stating that 50 out of 75 were cured, it looks like they had better results. In fact, they had the same results.

An important aspect to consider when evaluating studies is how the study was conducted.

Example: Brand A is the only available drug. Brand A's label directed everyone to receive 100 mgs. As time passed, physicians noticed that Brand A did not help people who were overweight. They did some studies and learned that overweight people needed higher doses. The FDA allows physicians to do this even if the drug's label does not specify it.

Along comes Brand B. In its clinical trials, the doses for Brand B were determined based on peoples' weights. Naturally, Brand B wants to prove that it is better than Brand A. Brand B conducts a clinical trial comparing participants taking each drug – a *head-to-head* study. However, the study design is flawed in favor of Brand B. Everyone taking Brand A will get the dose that is on the label – regardless of their weight. Everyone on Brand B will get a dose that matches his or her weight. If there are many heavy people in the study, then those getting Brand B will get more medication.

When looking at research results, always compare apples to apples and oranges to oranges.

It is important to learn if the study results apply to you. For example, if a drug was studied using middle-aged men, is it also safe and effective for a 20-year-old woman? Studies of new drugs usually involve a population

Let's Get Technical: 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."

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 α 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 β 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

of similar people (*homogeneous population*). However, even a study that uses a homogenous population needs to be examined critically. For instance, what does it mean if a report claims that 50% responded to an HCV therapy? If everyone in the study had your genotype, then the results may apply to you. However, if everyone had a different genotype, then you cannot apply the results to your situation.

There are other apples-to-apples issues when analyzing and comparing study results. Let us look at two studies. Both have the same number of participants, all the same gender, age, genotype, viral load, ethnic background, and liver biopsy results. However, Study #1 enrolled subjects with only one disease – HCV. Study #2 enrolled subjects with histories of mild depression, heart disease, and so on. It would be no surprise if Study #1 had better outcomes. Be sure to compare yourself with those who are similar to you before applying results to your situation.

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.

• *Understanding Surveys*

Sometimes information is conveyed by way of surveys. Surveys are not evidence-based. Survey results may be misleading and should not be used to make medical decisions. However, surveys and polls may promote a product or an opinion, so knowing how to evaluate them is important.

Who is funding the web site from which you get your information? Advertising on a web site tells you who, but even websites without ads may be paid for by commercial interests.

How a question is asked may influence the outcome. For example, Alice takes a poll that asks, "Should we invest more money into access to better healthcare?" Most people will probably favor this. Alice's opponent Betty asks, "Should we raise taxes to fund big government by passing a healthcare funding bill?" Now people are likely to oppose this. However, both Alice and Betty will use the survey results to support their positions.

The survey sample size is a significant factor that may be misleading. For instance, if two people are asked their opinion about Brand X and they both liked it, then it looks like 100% of the people surveyed liked Brand X. However if two more people are surveyed and their opinion differs from the first two, then that number drops to 50%.

There is another way to manipulate statistics using sample size and perseverance. Brand A wants to be the best and hopes to claim that at least four out of five doctors recommend their product. They ask the opinions of five doctors. If only one endorses Brand A, they ask five more doctors. If only three of them recommend it, they keep asking until they get four out of five. The surveyor is under no obligation to tell you that they asked 100 doctors before finding the desired response.



Look for web sites that end in .gov or .org rather than .com

Watch for bias. Even well-meaning researchers are biased. Suppose a researcher wants to prove his/her belief that HCV patients who are optimists fare better during treatment than pessimists do. This may affect the outcome before the study even begins. The researcher suspects the answer before the study starts and is looking for proof to support that belief. In subtle ways, this prejudice may influence the study design, conduct, and interpretation of data. The best way to conduct a study is with no preconceived notion of the outcome.

● *The Internet as a Source*

The Internet is 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 (NIH), 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 publication dates.
- Information provided in chat rooms and discussion forums is frequently anecdotal and based on individual experiences, which often cannot be generalized to all people with the same condition.
- Question what you read. Does the research stand up to careful scrutiny?
- Do not 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.

● *The Bottom Line*

Most of us rely on numbers. Numbers seem black and white. After all, two plus two equals four. However, the reliability of numbers is only as good as the humans interpreting them.

So, how do we know what to trust? How can we separate fact from fiction? Here are some suggestions:

1. Look at the source. If statistics are used for commercial or political purposes, the numbers may have been spun. If the numbers come from a reliable medical journal, such as *Hepatology*, *New England Journal of Medicine*, or *Lancet*, it is likely that these have stood up to scrutiny.
2. Compare apples to apples. If the subjects in a study were all Caucasian males over the age of 40, then the information may not apply to a 20-year-old African American female.
3. Use critical thinking. Ask questions. Assume nothing. Challenge what you read.
4. Check the source of funding for the research. It is not objective research if the data for the product comes solely from the manufacturer. Data needs to be verified independently by more than one source before it can be considered reliable.
5. Do not let emotions get in the way of facts. It is disturbing to read about HCV.
6. Get a reliable second opinion to confirm your understanding of the research.
7. Seek opinions from others who respect evidence-based medicine. They may have already found the information you are seeking.
8. Keep an open mind. Do not form an opinion and look for the facts to conform to your opinion. This means you are biased too.

A FINAL WORD

Never let research tell you how you feel. If half of surveyed HCV patients report feeling fatigued, that does not mean you should or will feel fatigued. No lab test or research should ever tell you how you feel. Data may be reassuring, but it is not a substitute for your opinion about your health. It takes years of education and experience to become an expert in the field of research. This guide provides 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. As the saying goes, knowledge is power.

APPENDIX A:

Resources

Hepatitis C Support Project:
www.hcvadvocate.org

Informed Health Online:
www.informedhealthonline.org/evidence-based-medicine.61.en.html

Medline Plus Medical Dictionary:
www.nlm.nih.gov/medlineplus/mplusdictionary.html

Medline's Understanding Medical Research:
www.nlm.nih.gov/medlineplus/understandingmedicalresearch.html

National Institutes of Health (NIH):
www.nih.gov

NIH Clinical Trials Web site:
www.clinicaltrials.gov

Patient Inform:
www.patientinform.com

The Cochrane Collaboration:
www.cochrane.org

United States National Library of Medicine:
www.nlm.nih.gov

APPENDIX B:

Glossary

Abstract – a brief summary of important points of a research article or other text.

Adverse event – an undesired action or effect of an experimental treatment.

Anecdotal evidence – the collection of information based on clinicians' observations.

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.

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 research team or study participants know 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 test 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.

Citation – refers to the source of the information

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.

Direct-acting Antiviral - there are at least 4 categories of direct-acting antivirals—protease inhibitors, polymerase inhibitors (nucleoside and non-nucleoside inhibitors) and NS5a inhibitors. DAA's target and inhibit viral enzymes that are important for replication of hepatitis C.

Efficacy – refers to the drug’s effectiveness, i.e., if it works.

Endpoints – The outcomes used to judge the effectiveness of the treatments.

Evidence-based medicine – Used by medical providers, this is the practice of using solid research in order to formulate treatment recommendations.

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 a virus. HCV has 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).

Half-life – the period of time it takes for the concentration of a drug to decrease to half its original concentration in the blood.

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

HCV polymerase inhibitor – an agent that inhibits HCV replication by interfering with the virus’ polymerase enzyme.

HCV protease inhibitor – an agent that inhibits HCV replication by interfering with the virus’ protease enzyme.

Inclusion criteria – conditions that must be met in order to be eligible for a clinical trial.

Institutional review board (IRB) – an IRB is a group that has been formally designated to review and monitor 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.

Interferon-alfa – 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.

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 for 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.

Off-label – use of an FDA-approved drug for an indication other than that for which it was approved.

Open-label trial – a clinical trial in which doctors and participants know which drug is being administered.

P-value – a measure of probability that is reported with clinical trial results. The p-value indicates the likelihood the results obtained are not due to chance alone. Traditionally, a p-value of less than .05 is considered statistically significant or not likely due to chance alone.

Peer review – review of a clinical trial by experts who were not associated with the research. Looks at scientific merit, participant safety, and ethical considerations.

Pegylated interferon – a form of interferon that has a long half-life in the body and can be injected less often (typically a week). Pegylated interferon is approved for the treatment of HCV.

Placebo – a pill (capsule, liquid, or injection) that contains an inactive substance. It is compared to the experimental drug in *placebo-controlled* clinical trials.

Protease Inhibitor – an agent that inhibits viral replication by interfering with the virus' protease enzyme.

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.

Risk/benefit ratio – a measurement used to evaluate whether potential benefits outweigh potential risks.

Safety – refers to the drug's toxicity or side effects.

Single-blinded study – this refers to a study in which the participants do not know if they are receiving the test substance or the placebo. See *blind/double-blind study*.

Standard of care – the level of care that all persons with a particular illness should receive; the level below which care would be considered substandard.

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.

Triple therapy – use of three drugs 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 pegylated interferon, ribavirin and a protease inhibitor.

Treatment-naïve – 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.

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

APPENDIX C:

———— *Questions To Ask About Clinical Trials* ————

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 because 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 are my responsibilities as a participant?
- How long does the study last? How many visits are required? Are appointments at specific times or is the schedule flexible? 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)?

Hepatitis C Support Project
 Alan Franciscus
 Executive Director, Hepatitis C Support Project
 Founder, Editor-in-Chief, HCSP Publications
 C.D. Mazoff, PhD
 Webmaster, Managing Editor





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