AMGEN® Biotech Experience

Scientific Discovery for the Classroom

Clinical Trials: From Disease to Medicine

Student Guide

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INTRODUCTION

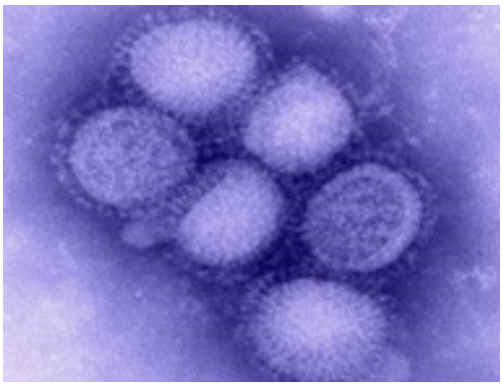
Infectious diseases have affected humanity from the beginning of recorded history. These plagues, called epidemics—a widespread occurrence of an infectious disease in a community at a particular time—often kill off large numbers of people. In the earliest days, an epidemic ended when the disease no longer had new people to infect; people lived farther apart, in remote pockets, and germ-spreading was cut off by the lack of intermingling. But in the age of discovery, as humans began to explore the world, they brought their ***endemic diseases*** (a disease or condition regularly found among particular people or in a certain area) to new populations. These new groups of people had no exposure to these pathogens and no immunity; thus, they were ravaged by the new diseases.

Today, pathogens can travel far and wide in very short periods of time, no longer contained by long travel times and isolated populations. These outbreaks are called ***pandemics***—global outbreaks of disease.

In 2009, a new pandemic arose: a virus called H1N1. Millions of people worldwide became infected at an alarming rate, and swift action was required to contain the spread of this disease.

By the end of the Introduction, you will be able to explain the following:

- The timeline of H1N1 and why it was cause for concern
- The differences between the three types of influenza
- Why genome sequencing is important for future treatment development



Transmission electron micrograph of the pandemic H1N1/09 influenza virus photographed at the CDC Influenza Laboratory.

YOUR TASK

It is 2009, and you are a clinical researcher overseeing the development of a promising vaccine to stem the H1N1 outbreak. It is important that you learn more about how the virus emerged and how it is infecting people to be able to test your vaccine and save lives.

April 2009: A New Flu Virus Emerges

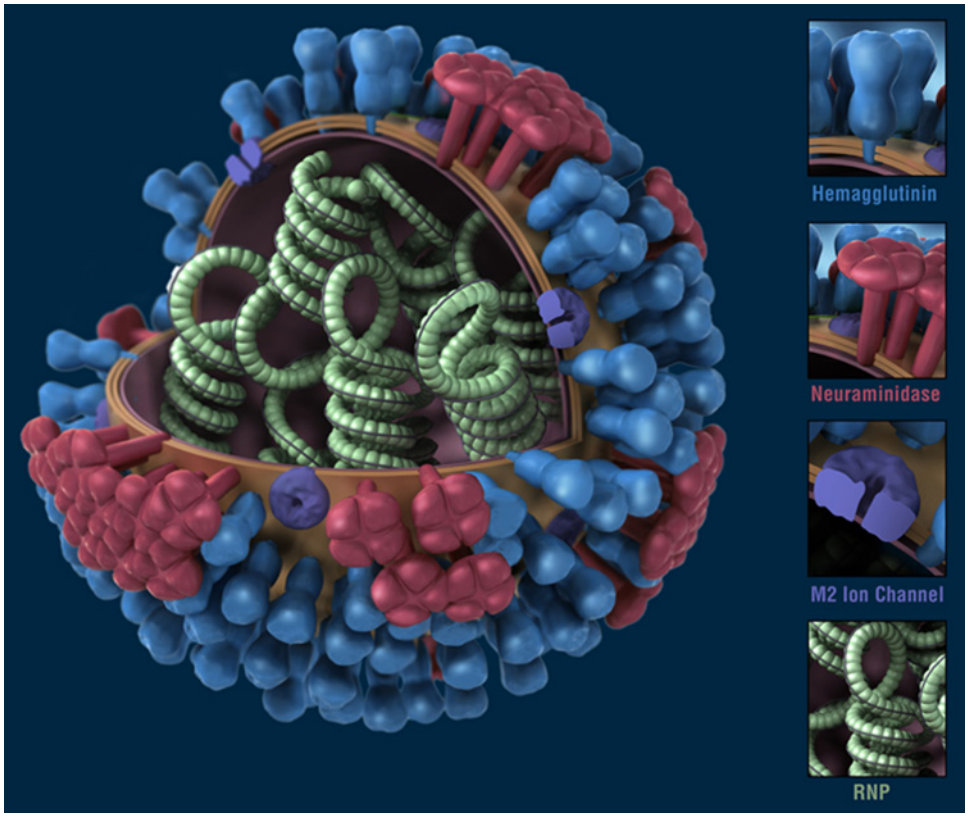
Influenza (flu) viruses that infect humans can be classified into three main groups: A, B, and C.

- Type A influenza infection can be serious and cause widespread outbreaks and disease. Type A flu is capable of infecting both humans and animals and is constantly changing.

- Type B influenza is found only in humans and cannot cause pandemics.
- Type C influenza is also found only in humans and causes much milder symptoms than Type A or B.

SO, WHAT DOES H1N1 MEAN?

In 2009, a new strain of the Type A influenza virus emerged, which scientists named H1N1. The designation "H1N1" represents unique characteristics of the virus that help our immune system distinguish it from other viruses. The "H" (hemagglutinin) and the "N" (neuraminidases) are proteins found in the outer part of the virus, sometimes called the envelope. Different viruses have different proteins. In this example of H1N1, the first "1" represents the known type of hemagglutinin and the second "1" represents the known type of neuraminidase.



3D graphical representation of the biology and structure of the 2009 H1N1 virus. Source: CDC

15 April 2009: Patient A Is Identified

The first human H1N1 virus infection is detected in California. Patient A, a 10-year-old resident of San Diego, arrives at the hospital with a number of symptoms, including fever, nausea, and sore throat. Lab results show that the symptoms are caused by a new flu virus known as H1N1, an influenza virus combining swine, avian (bird), and human genes that mutated in pigs and spread to humans.

17 April 2009: A Second Patient

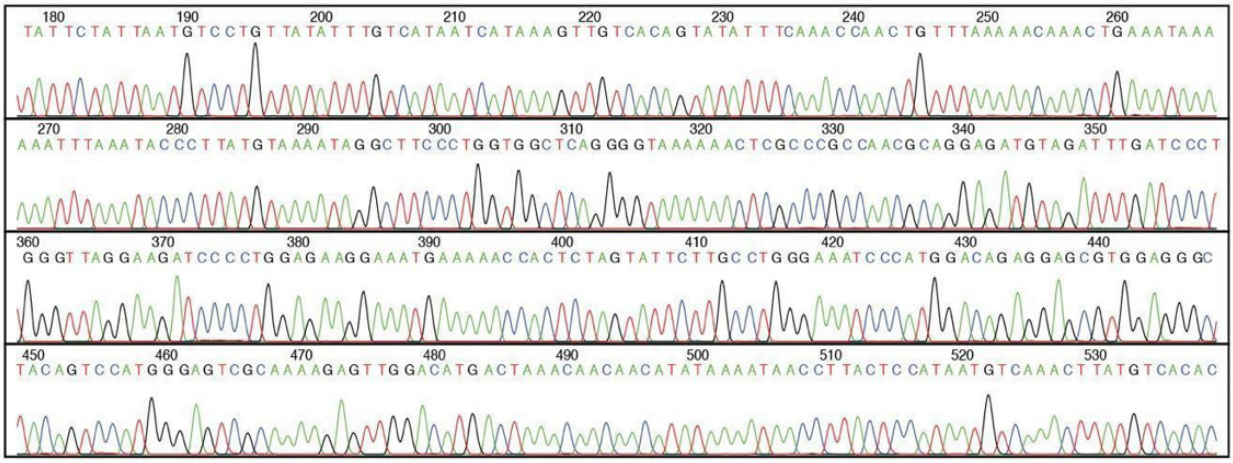
A second human infection with the H1N1 virus was detected in California about 130 miles away from the first infection, with no known connection to the previous patient.

With two California patients and a potential nationwide outbreak, the U.S. Centers for Disease Control and Prevention (CDC) begins working to develop a ***candidate vaccine virus***—a virus that has been prepared by the CDC or another public health partner and can be used by vaccine manufacturers to offer a public prevention method.

Lab techs work to assist the CDC in keeping a database of all known viruses.

24 April 2009: The Genome Is Sequenced

The CDC uploads the complete gene sequences of the 2009 H1N1 virus to a publicly accessible international influenza database. Below is an image of what a computerized genome sequence looks like.



GENOME SEQUENCING

A virus's ***genome*** consists of all the genes that make up that virus. The CDC conducts year-round surveillance of currently circulating influenza viruses to monitor changes to their genome (or parts of their genome). Genome sequencing reveals the sequence of the nucleotides in a gene, like letters in words. You may remember that *DNA* ***sequencing*** is the process of determining the sequence of nucleotide bases (As, Ts, Cs, and Gs) in a piece of DNA. Today, with the right equipment and materials, sequencing a short piece of DNA is relatively straightforward. But sequencing an entire genome (all of an organism's DNA) remains a complex task. It requires breaking the DNA of the genome into many smaller pieces, sequencing those pieces, and assembling the sequences into a single long "consensus."

INFLUENZA VIRUSES

Influenza viruses can change in two different ways: antigenic drift and antigenic shift. ***Antigenic shift*** occurs when two or more strains of a virus, or strains of two or more different viruses, combine to form a new type of virus that contains a mixture of the two or more original strains. ***Antigenic drift*** is more common; it refers to small, gradual changes that occur through mutations in the genetic material that cause small changes in the surface proteins hemagglutinin and neuraminidase. Antigenic drift produces new virus strains that may not be recognized by the immune system, even if it has been primed (by vaccination or prior infection) to recognize other influenza strains. A person infected with a particular influenza strain creates antibodies that recognize that strain of the virus, but if a new strain appears, the older antibodies will not recognize it, causing the person to become sick again. This is one reason that a person may get the flu more than once during flu season and why it is important to create vaccines against the viruses that are currently circulating among the population.

Since influenza viruses are constantly mutating, this work is performed as part of routine U.S. influenza surveillance and as part of CDC's role as a World Health Organization (WHO) Collaborating Center for Reference and Research on Influenza. The information the CDC collects from studying genetic changes (also known as ***substitutions***, ***variants***, and ***mutations***) in influenza viruses plays an important public health role; it helps to determine whether vaccines and antiviral drugs will work against currently circulating influenza viruses and the potential of new influenza viruses, currently circulating in animals, to infect humans.

Because the H1N1 virus is a new strain of influenza, the existing vaccines against seasonal flu provide no protection against it.

22 July 2009: Clinical Research Begins

In response to the H1N1 pandemic, researchers worked rapidly to develop treatments. A number of clinical trials were conducted to test various vaccines, resultingin two that were thought to be effective and deserved further evaluation.

In the late 1800s, treating a disease could be pretty haphazard. People devised their own remedies to manage and treat illnesses, with widely varying results—including the death of the patient from the treatment and not the disease! Today, we have standard procedures for ensuring the safety and efficacy of treatments and vaccines. You will learn more about these procedures in Chapter 4.

In preparation for Chapter 1, read **Two Types of Clinical Research** on page 10 and be prepared to discuss the Stop and Think questions with your class.

CHAPTER 1

PREPARING TO TEST THE VACCINE

OVERVIEW

In the Introduction, you learned about a new pandemic, H1N1, that is infecting millions of people worldwide at an alarming rate. You were introduced to a timeline of the virus, how it emerged, and what steps have been taken thus far to stop it. However, rates of infection are steadily increasing, and the need for a vaccine is more urgent than ever. In this chapter, you will learn about the important role of clinical research in treating and preventing disease.

CHAPTER 1 GOALS

By the end of this chapter, you will be able to do the following:

- List and describe the two major types of clinical research
- Describe the different types of clinical trials and the importance of each
- Explain the important role that placebos play in clinical research

WHAT DO YOU ALREADY KNOW?

Record your responses in your science notebook, and be prepared to discuss them with the class. Don't worry if you think you don't know the answers. Discussing these questions as a group will help you review what you already know about viruses, clinical research, and preventive treatments.

1. What is a ***candidate vaccine virus***, and why is it important?
2. Why does the CDC collect ongoing data about the influenza virus? How can this information help us with the current H1N1 outbreak?
3. What is the importance of uploading a virus's genome to an international database?

YOUR CHALLENGE

To move ahead with your task of overseeing the development of the new vaccine, you need to understand as much as you can about clinical research (medical research involving people) so that your team can decide which type is appropriate for this pandemic. There are two types of clinical research: observational studies and clinical trials. Read the descriptions of each below and then decide which type your team should use.

Two Types of Clinical Research

Observational studies involve monitoring people in normal settings. Researchers gather information, group volunteers according to broad characteristics, and compare changes in the groups over time. For example, researchers may observe several groups of older adults over time to learn more about the effects of different lifestyles on cognitive health via medical exams, tests, and/or questionnaires. These studies may help identify new possibilities for clinical trials.

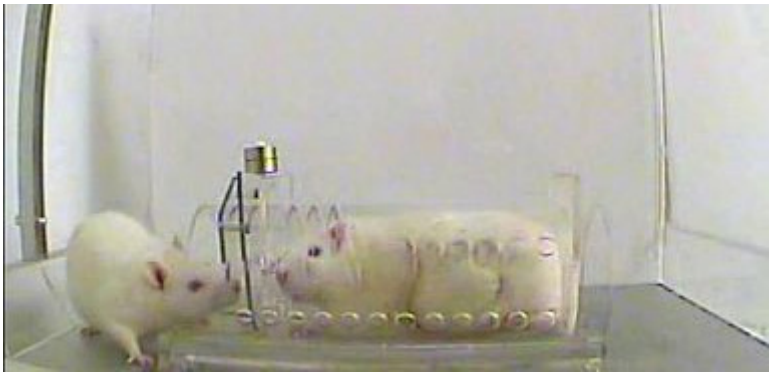
Clinical trials are research studies that investigate how effective a medical treatment or device is for treating a condition. They are the primary way that researchers find out if a new treatment—like a new drug, diet, or medical device (for example, a pacemaker)—is safe for human use and effective in treating an illness. Often, a clinical trial is used to learn if a new treatment is more effective and/or has fewer harmful side effects than the standard treatment.

Other clinical trials test ways to find a disease early, sometimes before there are symptoms, or to prevent a health problem. A clinical trial may look at how to make life better for people living with a life-threatening disease or a chronic health problem. Clinical trials may also study the role of caregivers or support groups.

STOP AND THINK 1.1

- Based on the above information, which type of clinical research will you run?
- What is the difference between the two types of research? Why would both be necessary?

Before the U.S. Food and Drug Administration (FDA) approves a clinical trial to begin, scientists perform laboratory tests on animals to determine a potential therapy's safety and efficacy. This is considered pre-clinical research. If these studies show favorable results, the FDA gives approval for the intervention to be tested in humans, which is known as ***clinical research***.



Source: National Institutes of Health

All clinical trials follow a predetermined protocol—a plan that details what researchers will do in the study, who may participate in the trial, the length of the study, and the schedule for tests, procedures, medications, and dosages.

TYPES OF CLINICAL TRIALS

There are different types of clinical trials, and each type serves a specific purpose. Your team will need to determine which type you will carry out to test the H1N1 vaccine. Below are a few examples of clinical trials:

Treatment Trials: Researchers test experimental treatments, new combinations of medicines and other drugs, or new approaches to surgery or radiation therapy.

Prevention Trials: Researchers look for better ways to prevent disease in people who have never had the disease, particularly those who may be at higher risk for developing it, or to prevent a disease from returning. These approaches may include medicines and other drugs, vaccines, vitamins, minerals, and lifestyle changes.

Quality-of-Life Research: Researchers explore ways to improve the comfort of and quality of life for individuals with a chronic illness.

DID YOU KNOW?

Scientists have identified that the psychological mechanisms of the placebo effect lie in both conscious expectations and learning. When we expect a drug to reduce pain levels, our brains release endogenous endorphins that in turn are responsible for alleviating pain. Researchers have identified a specific region in a higher functioning area of the brain (the mid-frontal gyrus) that seems to be linked to the placebo effect. We also integrate environmental and social cues (e.g., the oven timer dings), which generates an internal expectation ("I'm about to be fed!") and subsequent unconscious placebo response (my stomach growls, my mouth waters).

Sometimes people involved in research can bias an experiment's outcomes—either intentionally or unintentionally. Intentional bias constitutes misconduct and can irreparably harm the study and the researcher involved. Unintentional bias can stem from a study being incorrectly designed (for example, not using a large enough or varied enough sample) or from people (either researchers or participants) believing that an experiment should work and thereby influencing the results by seeing or experiencing what they expect to see or experience.

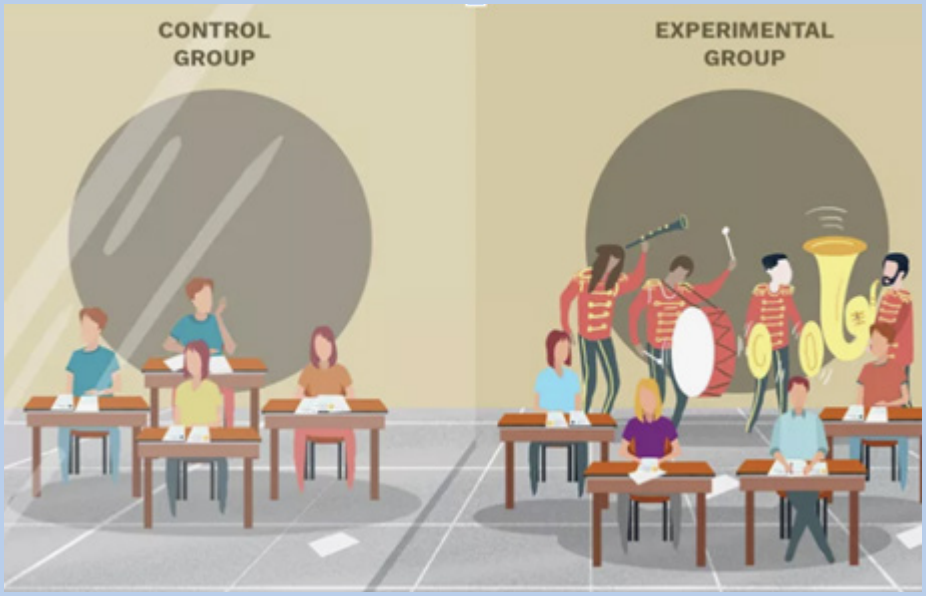
To help ensure that they are really studying the efficacy of their drug or therapy and not simply the perceived efficacy, researchers can choose to include a placebo in a clinical trial. A placebo is an inactive pill, liquid, or powder that physically mimics the process of taking the experimental drug but has no pharmacological effect.

When using a placebo, researchers may choose one of two methods to ensure that the results are not biased:

- In a ***blinded study***, the participants (subjects) do not know which treatment they are receiving.

- In a ***double-blinded study***, neither the participant nor the researcher knows what treatment the participant is receiving.

To use a placebo, researchers first must establish a control group. A ***control*** is the standard by which experimental observations are evaluated. One group of participants is given an experimental drug or treatment, and the control group is given either a standard treatment for the illness or a placebo, which can sometimes be no treatment at all.



In the experiment pictured, researchers are trying to determine whether distracting sounds affect student test scores. The control group takes the test normally, while a marching band plays in the room while the experimental group takes the test. Source: ThoughtCo.

Chapter 1 Question

Why do you think scientists test a new medication or therapy on laboratory animals before enrolling humans in clinical trials?

STOP AND THINK 1.2

- Based on the above choices, which type of trial do you believe that you and your team should run, and why? Think about your participants, how you will run the trial, and the details of what you will do. This will later become part of your team's protocol.
- Do you believe that a placebo will be necessary? Why or why not?
- Does it make sense to establish a control group?

Activity 1: Taking Part in Clinical Trials

You have learned so far that some trials focus on treatment, others on prevention, and some on quality-of-life research. However, it is also possible to conduct a clinical trial to simply gain a better understanding of the differences between humans or for educational purposes. In this activity, you will participate in a small clinical trial to explore the difference in sweetness between two types of candy.

NOTE: As this lab involves candy, if you have diabetes or sugar sensitivity, you should not participate and instead ask your teacher for an alternative activity.

1. Sit with your assigned team. Have one member of your team collect the materials for your taste-test experiment.
2. Each team member will silently perform the taste test and record their results.
3. Taste one of the candies, then swish your mouth with water. Taste the other candy. Immediately decide which candy tasted sweeter, and record your rating. Do not discuss your perception with your teammates!
4. After all team members have completed their taste tests, compare your data.
5. Add your team's data to the class histogram.

HOMEWORK

- Answer the Chapter 1 question.
- Read **Clinical Trials: An Overview** on pages 18–20 of Chapter 2, and be prepared to discuss the ***STOP AND THINK*** questions in the next session.

CHAPTER 2

WHAT HAPPENS IN A CLINICAL TRIAL?

OVERVIEW

In Chapter 1, you learned about the different types of clinical research—clinical trials and observational studies. You also learned about the three types of clinical trials and the purpose of each, and you were introduced to placebos and how they work on the human brain. In this chapter, you will learn about what happens during a clinical trial, the benefits and risks to participants, and some ethical issues that you and your team need to consider as you move forward with your research.

CHAPTER 2 GOALS

By the end of this chapter, you will be able to do the following:

- Describe what happens during a clinical trial
- Explain why it's important to consider ethical issues when conducting a clinical trial
- List some risks and benefits of participating in a clinical trial
- Explain why participant recruitment efforts for clinical studies must be clear and not misleading

WHAT DO YOU ALREADY KNOW?

Record your responses in your science notebook, and be prepared to discuss them with the class. Don't worry if you think you don't know the answers. Discussing these questions as a group will help you review what you already know about clinical research, placebos, and control groups.

1. What role does a placebo play in clinical research?
2. What is a control group, and why would it be used?
3. What does a clinical trial protocol consist of?

YOUR CHALLENGE

Before you can administer an experimental treatment in a clinical trial, you need to recruit and choose your participants. Who is your target audience, and what is the best way to appeal to these folks? Your team must create an advertisement for your clinical trial, one that will "sell" your trial to your target audience in an ethical manner.

Clinical Trials: An Overview

While each clinical trial is somewhat different, they all follow the same general steps:

1. Potential participants are recruited, given specific instructions for participating in the trial, and told how long the trial will last. They are informed of the risks and benefits of participation.
2. Participants sign an informed consent form, agreeing to take part in the trial. Their identifying information (such as name, date of birth, and home address) is kept in a locked file cabinet, and the participant is assigned a number or code as identification during the study so that no personal information is shared.
3. At the beginning of the trial, researchers check the health of each participant.
4. During the trial, participants are carefully monitored. Some clinical trials involve more tests and doctor visits than the participant would normally have for a particular illness or condition.

For all types of trials, the participant works with a research team, which includes doctors, nurses, researchers, social workers, and other healthcare professionals. Clinical trials are most successful when participants carefully follow the protocol and there is frequent contact between the research staff and participants.

CHOOSING PARTICIPANTS FOR A CLINICAL TRIAL

To decide who will be able to participate in your team's clinical trial, you first need to determine what criteria will allow participants to be included or excluded.

- Criteria for inclusion or exclusion are based on factors such as age, gender, type and stage of disease, previous treatment history, and/or other medical conditions.
- ***Inclusion criteria*** are the characteristics or conditions that prospective subjects need to have. Participants must meet all the inclusion criteria to be included in a study. The participants that you intend to include are your ***target population***.
- ***Exclusion criteria*** are those characteristics or conditions that disqualify prospective subjects from inclusion in the study. Even if they have just one exclusion criterion, they are out.
- The inclusion and exclusion criteria are not meant to reject people but rather to identify appropriate participants and keep them safe.

Think about the inclusion and exclusion criteria you will want for your clinical trial. To clearly market your clinical trial and to obtain informed consent, you will need to answer the following questions:

- Who is your target population?
- What are the risks and benefits of participating in this trial?
- How will you use this information to recruit participants?

BENEFITS AND RISKS OF PARTICIPATING IN A CLINICAL TRIAL

The benefits of participating in a clinical trial are many. Participants may obtain expert medical care at a leading healthcare facility during the trial, gain access to new research treatments before they are widely available, play an active role in their own healthcare, and help others by contributing to medical research. Some trials compensate participants with cash or gift cards.

Participation also carries potential risks. Some risks are relatively minor—for example, the study could take more of a participant's time and attention than regular treatment would, requiring trips to the study site, more treatments, hospital stays, or complex dosage requirements. But other risks include ineffective treatment and serious or even life-threatening side effects.

In actuality, no clinical trial comes without risk. One of the more famous clinical trials that went wrong happened in the early 1960s. The drug thalidomide was first manufactured in Germany, primarily for the purpose of treating respiratory infections. Today, many people know about this drug because of its adverse effects on pregnancy. Over 10,000 children born during the 1960s suffered serious impairments, such as missing limbs and cleft palates, as a result of their mothers taking this drug during pregnancy.

Adults born with deformities because of their mother's use of thalidomide without knowledge of the potential consequences to their unborn babies. Source: National Institutes of Health

The eerie part of the thalidomide clinical trial was that everything seemed to go right during the patenting and approval phase, when researchers tested the drug on animals. They determined that it was impossible to die from an overdose of the medicine, so it was deemed safe, and thalidomide hit the shelves in 1956. In a dreadful oversight, the researchers had neglected to observe the effects of thalidomide on the test animals' offspring.

It was not until 1961 that Australian doctor William McBride discovered the link between thalidomide and deformities during pregnancy. Up until then, every clinical trial had concluded that thalidomide was a safe over-the-counter medicine—and 10,000 people paid the price.

INFORMED CONSENT

Before participants can begin a clinical trial, they must read and sign an informed consent document that includes details about the study, such as the purpose, duration, required procedures, and risks and potential benefits of participation. The goal is to give potential participants enough knowledge to make a fully informed decision to participate. Participants then decide whether

to give their informed consent. The signed document confirms that participants agree to the stated conditions. The completed document is kept in a safe, secure location.

STOP AND THINK 2.1

- Why do you think human subjects are required to sign informed consent forms?
- Why might a person choose not to sign the informed consent form?
- Have you ever been part of a research study? Did you sign an informed consent form?

Ethical Considerations

Historically, men were the primary participants in early phases of clinical trials. From 1977 through the early 1990s, women of childbearing age were excluded from many studies to protect a potential fetus. Women were also excluded due to concerns over how their hormonal changes might affect study results. Leaving women out of research studies led to huge gaps in data regarding diseases and conditions common in women.

This exclusion has since been addressed by the National Institutes of Health (NIH) and other funding agencies, which has led to an increase in the participation of women in all phases of clinical trials. (You will learn more about clinical trial phases in Chapter 4.)

Diversity in general is important in clinical research. A diverse group of participants in a study allows researchers to see how interventions affect individuals of different ages, races, ethnicities, and genders, thus making medical products safer and more effective for everyone. NIH requires all federally funded clinical research studies to include women and minorities; however, minority populations are still underrepresented among trial participants, often due to economic, linguistic, cultural, religious, or geographic barriers. In addition, informed consent is itself an ethical issue; some research has found that people *don't* fully understand what they're getting into a lot of the time, and many feel pressured to consent.

STOP AND THINK 2.2

- Would having an inclusion criterion mean that you could or could not be involved in the trial?
- Which of the following would not be a criterion?
  - Age
  - Gender
  - Previous medical condition

Chapter 2 Questions

- Why do researchers use numbers or codes instead of human subjects' real names?
- What are some ethical issues to consider when doing research on humans, and how does having a control group affect this?
- Why is the use of a placebo ethical in some cases and not in others?

Activity 2: Advertising Your Trial

With your team, you will create an advertisement for your clinical trial.

1. Think about your target audience. Who can participate in your clinical trial, and what is the best way to appeal to these folks? What will the trial entail? Will participants be compensated? What other relevant information should you include?
2. Draft some text for your advertisement, and determine whether it is ethical. Are your statements accurate? Is anything misleading or easy to misunderstand? Keeping your inclusion criteria in mind, is your message likely to appeal to a diverse audience?
3. Use the chart paper provided by your teacher to create an advertisement for your trial. Remember, you want it to attract participants, so use bright colors and write clearly.
4. Display your completed advertisement in the classroom.
5. Do a gallery walk, and review other teams' advertisements. Think about what you have learned as you review each advertisement, and note any issues that are cause for concern.
6. Be prepared to answer questions and discuss any concerns about your team's advertisement.

HOMEWORK

- Answer the Chapter 2 questions.
- Read **What Is an Institutional Review Board?** on pages 25–27 of Chapter 3, and be prepared to discuss the ***STOP AND THINK*** questions in the next session.

CHAPTER 3

REGULATIONS FOR CLINICAL TRIALS

OVERVIEW

In Chapter 2, you learned about what happens during a clinical trial, risks and benefits involved in participation, and some important ethical issues to consider. This chapter introduces the important role of an Institutional Review Board and the compliance and safety regulations that must be met to begin a clinical trial.

CHAPTER 3 GOALS

By the end of this chapter, you will be able to do the following:

- Explain what an Institutional Review Board is and why it is important
- Describe the process of recruiting and screening participants for a clinical trial

WHAT DO YOU ALREADY KNOW?

Record your responses in your science notebook, and be prepared to discuss them with the class. Don't worry if you think you don't know the answers. Discussing these questions as a group will help you review what you already know about what happens during a clinical trial and how ethical issues are relevant to participant selection.

1. What is the difference between inclusion and exclusion criteria? Why are both necessary?
2. What are some risks to consider when participating in a clinical trial?
3. What is an example of an ethical issue that should be considered when determining what participants will be asked (or not asked) to do?

YOUR CHALLENGE

To ensure participants' safety and compliance with the institution's regulations, an Institutional Review Board is necessary. You will need approval from the Institutional Review Board before you can begin your clinical trial. Part of that approval depends on your recruitment of participants. In this chapter, you and your team will have an opportunity to design an advertisement for your clinical trial using ethically sound recruitment strategies.

What Is an Institutional Review Board?

The Institutional Review Board (IRB) is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted by the institution's staff.

The IRB is responsible for reviewing all research involving human participants prior to its commencement. The IRB is concerned with protecting the welfare, rights, and privacy of human subjects. It has the authority to approve, reject, monitor, and require modifications in all research activities that fall within its jurisdiction, as specified by both federal regulations and institutional policy. The IRB must have at least five members of varying backgrounds to provide complete and adequate review of human research and its institutional, legal, scientific, and social implications. The IRB also should include at least one member who is not affiliated with the institution and at least one member who is not a scientist.

BEFORE INSTITUTIONAL REVIEW BOARDS: THE INFAMOUS TUSKEGEE STUDY

The Tuskegee Study of Untreated Syphilis in the African American Male began in 1932 in Tuskegee, Alabama. Conducted by the U.S. Public Health Service (USPHS), a government agency, the study was designed to determine the natural course of untreated syphilis, a sexually transmitted infection. Four hundred Black men aged 25–60 who already had syphilis were followed, along with 200 uninfected subjects who served as a control group.

There were *many* problems with this study. For example:

- The subjects were recruited with misleading promises of "special free treatment"; they were not given all the facts required to provide informed consent. They also weren't informed that they had syphilis; instead, they were told that they were receiving treatment for "bad blood."
- In truth, subjects got no treatment. Many thought, or were misled into believing, that a spinal tap (a study of fluid in their spinal column) was treatment, but it was not. Participants were given ineffective medicines (ointments or capsules containing inadequate doses) to further their belief that they were being treated.
- Throughout the experiment, USPHS actively worked to ensure that the subjects did not receive treatment that could save their lives. When antibiotic therapy (penicillin) became widely available in the 1950s, the human subjects were not told that an effective treatment was available. The USPHS actively sought to prevent the subjects from getting the antibiotic.

By the 1970s, 128 participants had died of syphilis or its complications, 40 of their wives had been infected, and 19 of their children had acquired congenital syphilis.

In 1972, the Associated Press ran a story alerting the public to the study and its unethical practices. Due to the public outrage generated by the story, the government organization overseeing the study appointed an advisory group to review it. The advisory group concluded that the study was "ethically unjustified"—meaning that the risks to the subjects were far greater than the

knowledge gained—and advised that the study be terminated immediately. Families of the involved men filed a class action lawsuit and were awarded $10 million in an out-of-court settlement.

Largely in response to the Tuskegee study, on July 12, 1974, Congress passed the National Research Act, establishing IRBs to review *all* biomedical and behavioral research involving human subjects. In 1997, then-President Clinton apologized to the families on behalf of the nation.

STOP AND THINK 3

- How would you describe the historical importance of an Institutional Review Board?
- Why is it important to have an Institutional Review Board review all experiments involving human subjects?

Activity 3: Recruiting for a Clinical Trial

In this activity, you will role-play the recruitment process for a clinical trial, with two "clinicians" interviewing potential "participants" about their health histories.

1. Choose two members of your team to act as a team of clinicians who will choose participants for a clinical trial. The remaining students will act as potential participants.
2. **Participants:** Look over the note card that tells you about the role you are playing—including your age, sex, health history, and general information. Use this information to answer the questions the clinicians ask you. Remember, you are playing a role; answer the questions based on the details on your note card and not on your own personal information.
3. **Clinicians:**
    - o You will receive a clipboard, a list of the inclusion and exclusion criteria for the study, and a sheet of paper to record which participants are included and which are excluded.
    - o Interview each participant, using the inclusion and exclusion criteria to help inform your questions.
    - o As you record each participant's information, be sure to identify them by the ID number on their card and not their name.
    - o As you complete each interview, decide whether to include or exclude the participant.
    - o When you have interviewed all 10 participants, inform them who you included, who you excluded, and why. Be prepared to explain your reasoning.

4. Create a T-chart on the chart paper, listing the participant numbers of those who are included on one side, and those who are excluded on the other side. Include a brief note next to each participant number of why they were included or excluded.
5. Post your chart, and share your reasoning with the rest of the class.
6. Consider how this activity relates to obtaining IRB approval for a clinical trial.

HOMEWORK

- Read **The Four Phases of Clinical Trials** and **Why Does a Clinical Trial Take So Long?** on pages 32 and 33, respectively, of Chapter 4.

CHAPTER 4

PHASES OF CLINICAL TRIALS

OVERVIEW

In Chapter 3, you learned about the importance of having an established Institutional Review Board for all clinical trials, and how the Tuskegee Study impacted the way that research is conducted today. In this chapter, you will explore the different phases of clinical trials and why clinical trials can take a long time. You will have an opportunity to explore some current clinical trials to see how they are set up and how they market themselves for recruitment purposes. With your team, you will use all of this information as you complete an application for approval of your clinical trial for the H1N1 vaccine.

CHAPTER 4 GOALS

By the end of this chapter, you will be able to do the following:

- Describe the four phases of clinical trials and how they are different from one another
- Use an NIH website to explore ongoing clinical trials
- Complete an application for approval of a clinical trial

WHAT DO YOU ALREADY KNOW?

Record your responses in your science notebook, and be prepared to discuss them with the class. Don't worry if you think you don't know the answers. Discussing these questions as a group will help you review what you already know about the role of an IRB, how research is conducted and approved today, and why it's important to consider ethical issues when recruiting participants.

1. What are some examples of recruitment strategies that would be considered unethical?
2. What impact did the Tuskegee Study have on research conducted today?
3. Who makes up an Institutional Review Board?

YOUR CHALLENGE

You and your team are almost ready to begin your trial, but you need to submit your application for approval. Part of your application includes identifying which phase of clinical trials you are beginning. If you choose to start a Phase II clinical trial, your team needs to draft a brief summary of the Phase I results first. If you choose a Phase III or Phase IV study, you need to consider what has happened with your study up to this point.

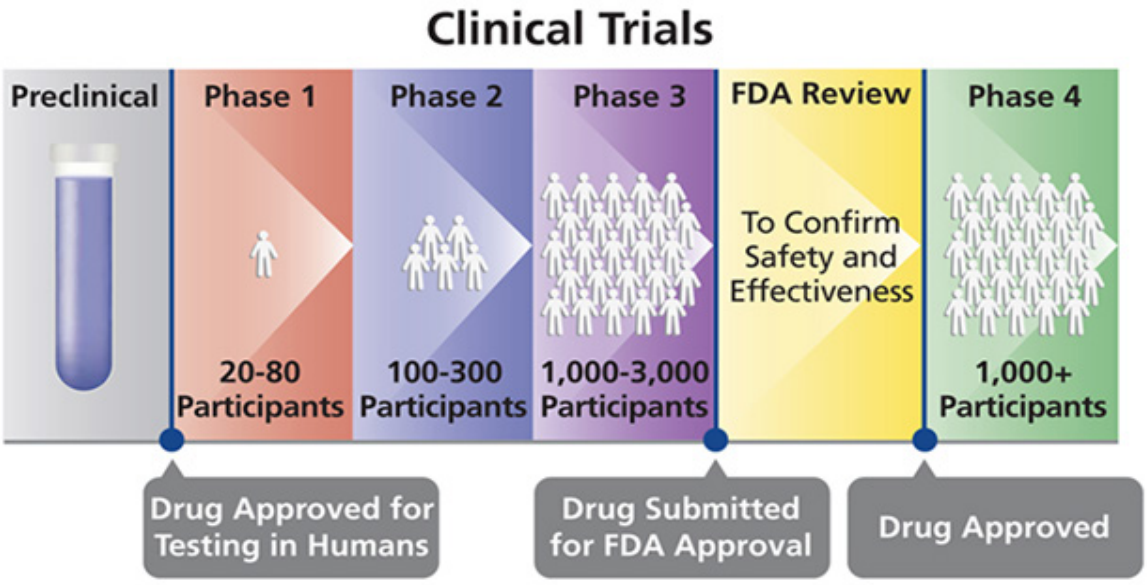
The Four Phases of Clinical Trials

Research on drugs or treatments can take place in four phases, designated by the Roman numerals I to IV. Each phase is a separate type of clinical trial. The goal of these trials is to establish the safety and effectiveness of an intervention.

Phase I involves testing a new drug's safety in the human body. Only a small number of participants are needed, usually healthy volunteers and individuals with similar diseases. In Phase I, the focus is more on the non-specific side effects associated with drug dosage. This phase also allows researchers to find the maximum dosage amount before side effects occur.

During **Phase II**, researchers test a drug's effectiveness and dosage among several hundred participants. Often there are two groups involved: the active treatment group, who is given an experimental drug or treatment, and the control group, who is given either a standard treatment for the illness or a placebo. Remember that a placebo is an inactive pill, liquid, or powder that has no treatment value. In clinical trials, experimental treatments are often compared with placebos to assess the experimental treatment's effectiveness.

Phase III involves measuring the drug or procedure against the best standard treatment. This is the last phase before submission to the FDA (U.S. Food and Drug Administration, the federal agency responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs) for approval. This phase involves significantly more participants than Phase II, in order to determine the scope of how effective the drug is under different circumstances and conditions.



Source: AIDSinfo, U.S. Department of Health and Human Services. (n.d.). Clinical Trial. HIV/AIDS Glossary. https://aidsinfo.nih.gov/understanding-hiv-aids/glossary/144/clinical-trial

In a **Phase IV** clinical trial, which occurs following FDA review, researchers study the side effects caused over time by a new treatment after it has been approved and is on the market. Phase IV trials look for side effects that were not seen in earlier trials; they may also study how well a new treatment works over a long period of time. Phase IV clinical trials can include thousands of people.

The ethical and legal codes that govern medical practice also apply to clinical trials, which must follow a carefully controlled FDA protocol. When researchers report the results of the trial—at scientific meetings, in medical journals, and to various government agencies—individual trial participants remain anonymous (i.e., their names are not reported).

Why Does a Clinical Trial Take So Long?

You might be wondering why this process takes so long. It takes a long time to determine if a treatment or a vaccine is effective and even longer to ensure that it is safe. New medicines are constantly in development. However, the FDA has strict safety protocols regarding the steps that new drugs must go through before people can use them. Given that approximately 90% of pharmaceuticals fail their clinical trials despite passing animal studies and that there are thousands of chemicals whose effects on the human body are unknown, the ability to easily distinguish the harmful from the helpful can take time. Often, researchers also want to understand the long-term effects of these medications on the human body. To do so, they must observe the participants over time.

Activity 4: Applying to Conduct Your Clinical Trial

You are ready to conduct a clinical trial of your H1N1 vaccine, and your next step is to obtain FDA approval. With your research team, think about which phase you decide to begin and use the outline below (and all the information you have gathered thus far) to prepare your application. You will submit your completed application to your IRB (teacher) for approval.

To see examples of current clinical trials, visit the ClinicalTrials.gov website, a database of clinical studies conducted around the world.

Preparing Your Application for a Clinical Trial of an H1N1 Vaccine

1. **Research questions:** Your research questions guide your clinical trial and procedures. These questions help you know why you are doing this study and what variables you need to measure. Think about the following questions:
    - o What are you trying to figure out?
    - o Is there anything else you would want to know about your new vaccine before it is mass-produced and available for the general population?

    Write down your three research questions in your science notebook.

2. **Hypothesis:** You will need to make a hypothesis about each research question. Look at each question and ask yourselves: What do we expect to happen, or what do we think the answer will be?

   Write one hypothesis statement (a complete sentence) for each research question in your science notebook. Use these hypothesis statements as your next paragraph below your research questions.

3. **Target population:** You need to define your target population—the group of people who are important to your study. Some things to consider when determining your target population:

   - What are some characteristics of potential participants that you'll need to include? Justify why certain characteristics are important and why some are deal-breakers.
   - What ages will you include?
   - Do participants have to live in a particular area?
   - Do they have to make a certain amount of money or work at a certain type of job?
   - How many people should you have in your study?
   - Is gender a factor?

   Write a paragraph describing your target population.

4. **Variables of interest:** Researchers usually pick variables or factors that give them information to answer their research questions. When choosing a variable, make sure that its presence or absence will help to prove or disprove your hypothesis. Also, keep in mind that you have two different types of vaccines (one is a placebo) to use in this study.

   - How could you use these two types of vaccines to answer your research questions?
   - Would a control group be relevant here?

   Write a paragraph that describes how you plan to include or exclude variables or factors that will help you answer your research questions.

5. **Sample:** Researchers usually cannot include every single person they want to target in the study, so they use a representative sample of their target population.

   - If you're using a control group, how will you decide who goes into which group?
   - Should you randomly assign participants to a group, or is there some other way you want to decide?

   Describe the sample you will use for your research study in one or two paragraphs. Be sure to include all details of your sample. Remember, your sample is a small sub-group of your target population.

6. **Setting up your study:** Think about the process of your clinical trial.
    - What is the best way to get the information you need?
    - How would you gather this information?
    - How will you keep track of the information you get from your participants? Will you use participants' names?
    - How often would you test participants?
    - How long will the study last?

    In a few paragraphs, describe your study set-up, including details on the above questions.

7. **Informed consent:** Before your participants take part in your study, you must obtain their informed consent. Create a document to distribute to participants that explains the study, including its duration; what participants will be expected to do; and the risks and benefits of participation.

Be prepared to share your completed application with the class.

CHAPTER 5

GRAPHS TELL STORIES: EXPLORING DATA

OVERVIEW

In Chapter 4, you learned about the four phases of clinical trials, and you gathered the information needed to submit a clinical research application. In this chapter, you will work with your team to further investigate and analyze clinical trial data.

CHAPTER 5 GOALS

By the end of this chapter, you will be able to do the following:

- Discuss the strengths and limitations of using survey data in research to illustrate comparisons, and use Google Sheets for analysis
- Draw conclusions and inferences based on data analysis

WHAT DO YOU ALREADY KNOW?

Record your responses in your science notebook, and be prepared to discuss them with the class. Don't worry if you think you don't know the answers. Discussing these questions as a group will help you review what you already know about clinical research design.

1. What is the purpose of a research question, and how does it inform your hypothesis?
2. Why is it important to determine your target population prior to recruitment?
3. How does the study sample relate to your target population?

YOUR CHALLENGE

Your team will now take a closer look at data and how it can be used to draw conclusions and make informed decisions. You will explore data (either your own or from a published clinical trial), translate the information into graphs, analyze your findings, and effectively communicate them to your class.

Activity 5: Telling Your Data Story

The pharmaceutical industry uses data analysis during product development to better guide them in their decision-making of new drugs and treatments. In this activity, you will do something similar, learning how to analyze your data to uncover relationships between variables and make necessary recommendations. With your research team, you will present your findings to the class.

Check with your teacher to see which option your team will do.

Option A: Gather Your Own Data

1. Your first task is to develop your protocol. You need to determine the following:

   - Your research question(s)
   - A hypothesis for each research question
   - Your target population

   You also need to include an informed consent form, describing the study for your participants and listing the risks and benefits of being involved. Compile all of this information into a protocol, and obtain approval from your teacher.

2. Brainstorm some questions you will ask in your interviews, and then narrow the list to the five questions that you believe are most important in addressing your research question. Your interview questions should help you confirm your hypothesis, so make sure that you are asking questions relevant to what you want to find out.

   Here are some examples:

   - During the past week, how many hours of sleep/night did you get on average?
   - During the past week, how many days did you exercise, play a sport, or participate in a physical activity that made you sweat or breathe hard for at least 20 minutes?
   - On an average weekday, about how much time do you spend reading for pleasure?
   - On an average weekday, about how much time do you spend using a computer for purposes other than schoolwork?
   - On an average weekday, about how much time do you spend watching TV, watching videos, or playing video games?
   - Are there family rules about "screen time"—how much time you can spend watching TV or playing games on the computer?
   - Is there a TV in your bedroom?
   - On an average day, how many vegetables do you eat?
   - In an average week, how many home-cooked meals do you eat vs. take-out or fast food?

3. You are ready to begin gathering data! You and your team will interview and assess (using the physical fitness measures) 10 willing participants. Remember to obtain their consent and keep all identifying information confidential—no names should be used in this activity. Be sure to record data from both the interview and the physical fitness protocol.
4. Now it's time to analyze your results. You will need to input your data into Google Sheets to obtain a chart and then further analyze the data. See the directions *Using Google Sheets to Analyze Data.*
5. With your team, think about how you want to organize your data. Which types of graphical representations would best illustrate the connections between the data and the outcomes? Consider the following questions:
    - What factors had the greatest effect on the study outcomes?
    - What factors had the least effect on the study outcomes?

    Create two graphical representations of your data to share with the class.
6. Think about how to present your findings to the class. Consider the following questions:
    - What is the statistical significance of the data that you chose to represent?
    - Why did you choose the graphical representations that you did?
    - What about your findings surprised you?
    - Was your hypothesis confirmed by your data results?
    - What are some of the strengths and limitations of your survey?
    - How did your interview findings correlate with your physical fitness test findings?
    - Are your conclusions logical and supported by the data?
    - What were your biggest challenges to analyzing the data you obtained?
    - What recommendations regarding healthy habits would you make to high schoolers, based on your findings?

See the end of this activity for instructions on how to use Google Sheets to analyze data.

Option B: Examine Existing Clinical Data

1. Your team's first task is to choose a clinical study on ClinicalTrials.gov that focuses on H1N1. Using the filter option, choose a study from the ones available.
2. Review how your chosen study was conducted. Consider the following:
    - Who was the target population?
    - How many participants were included?
    - What treatment was being tested?
    - Was a placebo offered?
    - What was the outcome?
    - What were the overall findings?
    - Did the study present or uncover any additional challenges?

3. Your team's next task is to analyze the results of the clinical study.
    - Think about two graphical representations for your data. If graphs are provided as part of the clinical study report, be sure that you understand and analyze that data, as you will share these graphs with the class.
    - You may also choose to use Excel and input the data yourself to generate your own analysis (see the directions below).

USING GOOGLE SHEETS TO ANALYZE DATA

Begin by **creating a chart** using your data in Google Sheets:

1. On your computer, open a spreadsheet in Google Sheets.
2. Input your data.
3. Select the cells you want to include in your chart.
4. Click Insert Chart.

Next, choose your **chart type**:

1. Double-click the chart you want to change.
2. At the right, click Setup.
3. Under "Chart type," click the Down arrow.
4. Choose your charts from the list. *Remember, you will need to have at least two graphical representations.*

If you're creating a **pie chart**:

1. Double-click the chart you want to change.
2. At the right, click Customize.
3. Click Pie chart.
4. Under "Slice label," choose an option.

Now, you can decide on the **data ranges** you would like to include:

NOTE: The "data range" is the set of cells you want to include in your chart.

1. Double-click the chart you want to change.
2. At the right, click Setup.
3. Under "Data range," click Grid.
4. Select the cells you want to include in your chart.
5. Optional: To add more data to the chart, click Add another range. Then, select the cells you want to add.
6. Click OK.

You can also add **data labels** to a bar, column, scatter, area, line, waterfall, histograms, or pie chart.

1. Double-click the chart you want to change.
2. At the right, click Customize > Series.
3. Check the box next to "Data labels."

Tip: Under "Position," you can choose if you want the data label to be inside or outside the bar.

Adding Text Notes to a Data Point

1. In the column to the right of each data point, add your text notes.

   **If your notes don't show up on the chart, go to Step 2.*

   Example

   - Column A: Labels for horizontal axis
   - Column B: Data points for vertical axis
   - Column C: Notes

A	B	C
Day of Week	Sales	Notes
Monday	50	Low profits
Tuesday	100	Online coupon announced

2 Add labels.

   a. Double-click the chart you want to add notes to.
   b. At the right, click Setup.
   c. In the box next to "X-axis," click More > Add labels.
   d. Enter the data range with your notes. For example, C2:C3.
   e. Click OK.

Finally, something interesting may be to add a **trendline**. This helps you see patterns in your charts. However, you can only add trendlines to bar, line, column, or scatter charts.

1. Double-click a chart.
2. At the right, click Customize > Series.
3. Optional: Next to "Apply to," choose the data series you want to add the trendline to.
4. Click Trendline. If you don't see this option, trendlines don't work with your data.

GLOSSARY

Antigenic drift: Small changes (or mutations) in the genes of viruses that can lead to changes in the surface proteins of the virus.

Antigenic shift: When two or more different strains of a virus, or strains of two or more different viruses, combine to form a new type of virus that contains a mixture of the two or more original strains.

Blinded study: A study where the participants (subjects) do not know which treatment they are receiving (active or placebo) but the clinician does know.

Candidate vaccine virus: A virus prepared by the CDC or another public health partner that can be used by vaccine manufacturers to offer a public prevention method.

Clinical research: Research designed to evaluate and test new interventions such as vaccines or medication.

Clinical trial: A research study that investigates how effective a medical treatment or device is for treating a condition.

Control group: A group of participants that closely resembles the treatment group, but this group does not receive the active medication or vaccine being tested and are instead given a placebo.

Double-blinded study: A study where neither the participant nor the researcher knows what treatment the participant is receiving (active or placebo).

Endemic disease: A disease or condition regularly found among particular people or in a certain area.

Exclusion criteria: Those characteristics or conditions that disqualify prospective subjects from inclusion in a study.

Genome: All the genes that make up a virus.

Inclusion criteria: The characteristics or conditions that prospective subjects need to have.

Mutations: Genetic changes that result in changing the genetic sequence, or DNA strand.

Observational study: A study involving observing people in normal settings.

Pandemic: A global outbreak of disease.

Sequencing: The process of determining the sequence of nucleotide bases (As, Ts, Cs, and Gs) in a piece of DNA.

Substitutions: Genetic changes.

Target population: The participants you intend to include in your study.

Variants: The diversity found in gene frequencies. This varies from individual to individual.