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Internet Archive
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# AFFIDAVIT OF CHRISTOPHER BUTLER

1. I am the Office Manager at the Internet Archive, located in San Francisco, California. I make this declaration of my own personal knowledge.

2. The Internet Archive is a website that provides access to a digital library of Internet sites and other cultural artifacts in digital form. Like a paper library, we provide free access to researchers, historians, scholars, and the general public. The Internet Archive has partnered with and receives support from various institutions, including the Library of Congress.

3. The Internet Archive has created a service known as the Wayback Machine. The Wayback Machine makes it possible to surf more than 450 billion pages stored in the Internet Archive's web archive. Visitors to the Wayback Machine can search archives by URL (i.e., a website address). If archived records for a URL are available, the visitor will be presented with a list of available dates. The visitor may select one of those dates, and then begin surfing on an archived version of the Web. The links on the archived files, when served by the Wayback Machine, point to other archived files (whether HTML pages or images). If a visitor clicks on a link on an archived page, the Wayback Machine will serve the archived file with the closest available date to the page upon which the link appeared and was clicked.

4. The archived data made viewable and browseable by the Wayback Machine is compiled using software programs known as crawlers, which surf the Web and automatically store copies of web files, preserving these files as they exist at the point of time of capture.

5. The Internet Archive assigns a URL on its site to the archived files in the format http://web.archive.org/web/[Year in yyyy][Month in mm][Day in dd][Time code in hh:mm:ss]/[Archived URL]. Thus, the Internet Archive URL http://web.archive.org/web/19970126045828/http://www.archive.org/ would be the URL for the record of the Internet Archive home page HTML file (http://www.archive.org/) archived on January 26, 1997 at 4:58 a.m. and 28 seconds (1997/01/26 at 04:58:28). A web browser may be set such that a printout from it will display the URL of a web page in the printout's footer. The date assigned by the Internet Archive applies to the HTML file but not to image files linked therein. Thus images that appear on a page may not have been archived on the same date as the HTML file. Likewise, if a website is designed with "frames," the date assigned by the Internet Archive applies to the frameset as a whole, and not the individual pages within each frame.

6. Attached hereto as Exhibit A are true and accurate copies of printouts of the Internet Archive's records of the HTML files for the URLs and the dates specified in the footer of the printout.

7. I declare under penalty of perjury that the foregoing is true and correct.

DATE: 12/2/16

Christopher Butler

CALIFORNIA JURAT

See Attached Document.

A notary public or other officer completing this certificate verifies only the identity of the individual who signed the document to which this certificate is attached, and not the truthfulness, accuracy, or validity of that document.

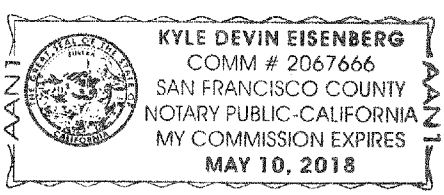
State of California
County of San Francisco

Subscribed and sworn to (or affirmed) before me on this

2 day of December, 2016, by

Christopher Butler,

proved to me on the basis of satisfactory evidence to be the person who appeared before me.




Signature: _____

A notary public or other officer completing this certificate verifies only the identity of the individual who signed the document to which this certificate is attached, and not the truthfulness, accuracy, or validity of that document.

STATE OF CALIFORNIA COUNTY OF _____

Subscribed and sworn to (or affirmed) before me on this_____ day of _____, 20____ by _____

_____

proved to me on the basis of satisfactory evidence to be the person(s) who appeared before me.

_____
(Signature of Notary)

# Exhibit A

# Lilly Clinical Trials


**Frequently Asked Questions**



## What is a clinical trial?

A clinical trial is a well-controlled research study testing a new investigational medication or therapy in humans. Before a clinical trial can begin, the FDA (Food and Drug Administration) must approve the use of the new drug for testing in humans. Clinical trials, required for all new drugs before they can be released for use in the general public, are generally organized into four phases: Phase I, II, III, and IV. You should understand which phase of testing the new drug therapy is in when you consider volunteering for a clinical trial.

**Phase I** A Phase I clinical trial is the first step in testing a new investigational medication in humans. Phase I studies are mainly concerned with how the drug is absorbed and broken down by the body. These studies help determine the best way to give a drug to a patient (for example by mouth, or by injection), and what side effects may be likely. Except for drugs used to treat cancer, Phase I clinical trials are usually conducted in healthy individuals and are not intended to treat disease or illness. Because cancer can be such a life-threatening condition, Phase I trials with anti-cancer drugs are usually carried out in patients who already have the disease.

**Phase II** Phase II clinical trials may involve up to several hundred volunteers who have the disease state or condition to be treated. These trials may last one to two years as physicians and researchers begin to learn more about the safety of the new drug treatment and how well it treats the disease or condition. Several different doses of the drug may be looked at to see which dose has the desired effects. Patients are watched for side effects and for any improvement in their illness, symptoms, or both.

**Phase III** After a drug has been shown to have positive results in small groups of patients, it may be studied in a larger Phase III trial. A Phase III trial usually compares how well the new drug works with a drug that has already been approved and has been used to treat the disease condition. One group of patients may receive the new drug being tested, while another group of patients may receive the comparator drug (already-approved drug for the disease being studied). And in some Phase III studies testing drugs that are not for life-threatening illness such as cancer, a third group of patients may receive a placebo "sugar pill". Patients in phase III trials generally do not know which drug they are getting, and in many cases, neither do the doctors. This is commonly referred to as a "blinded" study and this is done to make a fair evaluation in how well the new drug therapy works.

**Phase IV** Phase IV clinical trials are sometimes called "post-marketing" trials because these studies begin after the Phase I – III study results have been given to the FDA for approval. These studies usually enroll several hundred to several thousand patients and may be done to determine if the drug is effective against other disease states, or to test different ways of taking the drug such as tablets, time-release capsules or syrups.

## What are the risks associated with clinical trials?

Although a lot of research has been performed on each drug before it is given to humans, it is important to remember that clinical trials are conducted to learn more about how the drug will act in the human body. Clinical trials can help to determine if there are any side effects and if so, what to expect. The amount of risk depends on the type of study. Your physician will take the time to explain the potential risks with you, and will ask a lot of questions about your medical history to help reduce the risks. You have the right to receive answers to any questions you may have about volunteering for a clinical trial. To help you talk over any concerns with your physician, we have prepared a list of questions to ask, below.

## What are the benefits of participating in a clinical trial?

The decision to participate in a clinical trial is a personal one that may or may not include any direct benefits to you. Some of the potential benefits may include the opportunity to:

- Receive a new drug therapy that is not currently available.
- Receive professional medical care and free study medication for a disease condition you might already have.
- Contribute to society by helping investigate treatment options for a disease or illness.
- Receive compensation for your participation in the trial.

## What does it cost?

There should be no cost to participate in a clinical trial and study medication is free of charge.

## How do I find out about trials?

- Check your local newspaper for advertisements of clinical trial studies being done in your area.
- There are many World Wide Web sites on the Internet listing clinical trials that are looking for volunteers. You can do your own search by logging onto a search engine such as www.yahoo.com, www.altavista.com, or www.netscape.com, and include key words such as *clinical trials* or *clinical research*.
- Your physician or healthcare professional.
- Hospitals and Local Universities.
- Disease Associations such as the American Cancer Society, (check your phone directory for local chapters).

## What questions should I ask?

You have the right to receive answers to any questions you may have about volunteering for a clinical trial. There are no wrong questions. Listed below are some sample questions to help you talk over your concerns with a physician or healthcare professional:

- Why is this study being conducted? What are the goals of the study?
- What are my risks in participating in this trial?
- How will my participation be kept private?
- Will my study results be shared with anyone?
- How much time involvement will this require?
- Will I be asked to drive to a health clinic or hospital? How often?
- What about childcare arrangements during health clinic or hospital visits?
- What if I want to stop participating on this trial?
- Will I know what drug treatment, if any, I will be receiving?
- What if I feel ill when I am at home?
- Can I still take my birth control pills?
- Can I still take my other medications?
- What if I become pregnant?
- What happens if I am harmed by the drug treatment?
- How do the side effects of the new drug therapy differ from the standard treatments?
- Has this treatment ever been tested in humans?
- What if the test drug doesn't work and I am still sick?
- Who is in charge of my care?
- How can I reach a healthcare professional when I am at home?
- If I benefit from the new drug treatment, can I continue to receive the medication after the study is ended?
- Who is paying for the study? Will I receive any money for parking, etc.?
- Will I receive any money for participating in the trial? How much?
- Where does my medical insurance provider fit into this study?
- Will the study results be communicated to me? When?

# Lilly Clinical Trials


A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z

## L

**Labeling**
All labels and other written, printed or graphic matter upon any article or any of its containers or wrappers, or accompanying such article.

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z

## M

**Marketed drug**
A drug product for which marketing authorization has been granted.

**Multicenter trial**
A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

## N

No definitions

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z

## O

**Open-label study**
A study in which the investigator and the study participant are aware of the drug therapy received during the study.

## P

**Patient**
A study participant who has the disease or condition for which the investigational product is targeted.

**Patient files**
Hospital files, consultation records, or special patient files that are maintained and kept at the study site.

**Phase (in relation to drug development)**
Drug development is divided in phases that are determined by the main objectives of the drug development process.

- **Phase I** A Phase I clinical trial is the first step in testing a new investigational medication in humans. Phase I studies are mainly concerned with how the drug is absorbed and broken down by the body. These studies help determine the best way to give a drug to a patient (for example by mouth, or by injection), and what side effects may be likely. Except for drugs used to treat cancer, Phase I clinical trials are

usually conducted in healthy individuals and are not intended to treat disease or illness. Because cancer can be such a life-threatening condition, Phase I trials with anti-cancer drugs are usually carried out in patients who already have the disease.

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- **Phase IV** Phase IV clinical trials are sometimes called "post-marketing" trials because these studies begin after the Phase I – III study results have been given to the FDA for approval. These studies usually enroll several hundred to several thousand patients and may be done to determine if the drug is effective against other disease states, or to test different ways of taking the drug such as tablets, time-release capsules or syrups.

**Placebo**
An inactive substance used in controlled studies. The placebo may be used in screening or washout periods or used as a comparator to determine the efficacy of medical substances.

**Protocol**
An action plan for a clinical trial. The plan states what will be done in the study and why. It outlines how many people will take part in the study, what types of patients may take part, what tests they will receive and how often, and the treatment plan.

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z

## Terminology

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z

**Adverse Event (AE)**: An unfavorable or unintended sign, symptom, reaction, or disease that is associated in time with the use of an investigational drug, whether or not the event is related to the investigational drug, or is expected.

**Adverse Event, Serious (SAE) or Adverse Drug Reaction, Serious (Serious ADR)**: An adverse event that at any dose of the drug meets one of the following conditions:

- Results in death, or
- Is life-threatening, or
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

**Advertisement**: In clinical trials, recruitment advertisements are any materials used for recruitment of study participants (for example, letters, bulletin board notices, and notices in newspapers, or on radio, television, or the internet).

**Blinding**: A procedure in which one or more parties to the clinical trial (i.e., the subject/patient, investigator, and/or sponsor medical personnel) are kept unaware of the treatment assignment(s) of the clinical trial participants. Used to remove potential for study bias.

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**Clinical Trial / Study**: Any investigation in humans intended to discover or verify the effects of an investigational drug or new use of an already marketed drug, and/or to identify any adverse reactions to the investigational drug with the object of determining safety and/or efficacy of the studied use. The terms “clinical trial” and “clinical study” are synonymous.

**Clinical Trial Data**: All collected information arising from patients entering a clinical trial.

**Clinical Trial Material**: The testing material used in a clinical trial, including the primary study drug, comparator drugs, and placebo as specified in the study protocol. Clinical trial material includes any investigational product, including medical devices, designed for human use.

**Clinical Trial Material Package Lot Number**: An identification number associated with clinical trial material that identifies a batch of clinical trial material and from which the production and distribution history can be determined.

**Comparative Study**: A study in which a participant is randomly assigned to one of two or more treatment groups for purposes of comparing the results of the separate treatment groups.

**Comparator Drug**: An investigational or marketed drug (i.e., active control) or placebo used as a reference in a clinical trial.

**Completed Study**: For this registry, a study is considered completed on the date of the last patient visit (of the patients enrolled in that study) by an investigator authorized to conduct the study by the sponsor and the IRB/ERB.

**Confidential Information** : Information not in the public domain that is private to the study participant (such as identity or personally identifiable health information), or that is proprietary to the sponsor (such as intellectual property and some study designs and endpoints).

**Core Registration Studies**: Those primary safety and efficacy studies that the relevant government health agency uses to decide whether or not to approve the investigational drug or new use of a marketed drug. These studies are usually phase 3, always well controlled, randomized, of adequate size and, whenever possible, double blind. May also be called **Pivotal** or **Confirmatory** Trials.

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**Documentation**: All records, in any form (including without limitation written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken or omitted.

**Dosing Regimen**: The expected amount of study medication prescribed per time unit and duration of dosing (for example, 3 times/day for 7 days of therapy) as required in the study protocol.

**Double-Blind Study**: A clinical trial in which neither the investigator nor the study participant is aware of the treatment received.

**Drug**: Any recognized chemical compound that may be used on or administered to humans or animals as an aid in the diagnosis, treatment, or prevention of disease or other abnormal condition.

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**Efficacy**: The ability to produce a desired favorable effect in treating or preventing the studied disease or condition.

**Enroll**: The point at which a study participant is assigned to a study treatment in a clinical trial.

**Enter**: The act of obtaining informed consent for participation in a clinical study from participants deemed potentially

eligible to participate in the clinical study.

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**Food and Drug Administration (FDA)**: A branch of the U.S. Department of Health and Human Services primarily responsible for regulating the approval and use of drugs, medical devices, cosmetics, and foods.

**Good Clinical Practice (GCP)**: A standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are respected and protected.

**Healthcare Professionals**: Medical practitioners, pharmacists, dentists, nurses, and other individuals authorized to administer or dispense pharmaceutical products.

**Hypothesis**: A scientific idea about how something works, before the idea has been tested. Scientists do experiments to test a hypothesis and see if the hypothesis is correct.

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**Indication**: The efficacy claims that are approved by the relevant government health agency for the medicine on the basis of the Core (Pivotal) Registration Studies. The indication is contained in the product label, also called prescribing information. The indications for a product may (and often do) differ by geography and country.

**Informed Consent**: A process by which a participant voluntarily confirms his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the trial relevant to the participant's decision to participate, including known and potential risks and benefits. Informed consent is documented by means of a written, signed and dated informed consent form.

**Initiated Trial**: See Study Start Date.

**Institution (Medical)**: Any public or private entity or agency, or medical or dental facility, where clinical trials are conducted.

**Institutional Review Board, or IRB:** Also known in some countries as **Ethics Review Board**, or **ERB**. This is the scientific institution that is independent of the sponsor of the clinical trial that reviews and approves the study protocol on ethical treatment grounds and ensures that each participant enrolled in the trial has given their informed consent to participate. The IRB or ERB monitors the clinical trial from inception through completion.

**Investigational Drug**: An active drug that is being studied in a clinical trial.

**Investigational New Drug Application (IND)**: After completing preclinical testing, a company files an IND with the U.S. Food and Drug Administration to begin to test the drug in humans. The IND becomes effective if FDA does not disapprove it within 30 days. The IND shows results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the investigational drug; how it is thought to work in the human body; any toxic effects found in the animal studies; and how the compound is manufactured. All clinical trials must be reviewed and approved by the Institutional Review Board (IRB) where the trials will be conducted (in Europe, the Ethics Review Board, or ERB).

**Investigator**: A health care professional responsible for the conduct of a clinical trial at a trial site and who coordinates with the study sponsor and the IRB. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

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**Labeling**: All labels and other written, printed or graphic matter on a medication or any of the medication's containers or wrappers, or that accompany the medication, such as the prescribing information. The labeling of a medication includes a description of the uses for which the medication has been approved by the government for the geography where the drug will be marketed.

**Last Patient Visit**: The "Last Patient Visit" is considered the last study visit of the last patient remaining in the trial, anywhere in the world.

**Marketed Drug**: A drug product for which marketing authorization has been granted in at least one indication in a particular country by a government health agency. Once initial marketing approval is obtained, subsequent research may be ongoing for additional indications or formulations or as part of required safety follow up.

**Methodology**: The way in which information is found or something is done. The methodology includes the methods, procedures, and techniques used to collect and analyze information.

**Multicenter Trial**: A clinical trial conducted according to a single study protocol and identical methods at more than one investigative site, and therefore, carried out by more than one investigator.

**New Drug Application (NDA)**: Following the completion of all three phases of clinical trial development, a company analyzes all of the data and files an NDA with the U.S. Food and Drug Administration if the data successfully demonstrate both safety and effectiveness. The NDA contains all the scientific information that the company has gathered on the investigational drug. NDAs typically run 100,000 pages or more and can take up to a year or longer to review by the FDA, on average. Once FDA approves an NDA, the new medicine becomes available for physicians to prescribe.

**Observational Study**: A study in which the investigator does not manipulate the use of an intervention (e.g., do not randomize patients to treatment and control groups), but only observes patients who are (and sometimes patients who are not) exposed to the intervention, and interpret the outcomes. The investigator's decisions regarding the proper treatment and care of the patient are made in the course of normal clinical practice.

**Off-label Use**: The prescribing of a medication by a physician or other healthcare provider for a use other than that

which the medicine has been approved for marketing by a government health agency.

**Open-label Study**: A study in which the investigator and the study participant are aware of the drug therapy received during the study.

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**Patient**: A study participant who has the disease or condition for which the investigational product is being studied.

**Patient Files**: Hospital files, consultation records, or special patient files that are maintained and kept at the study site. In this context, also includes Phase 1 study participants, who are typically healthy volunteers without disease.

**Pharmacokinetics**: The actions of a drug in the human body over a period of time, including the absorption, distribution, metabolism, and excretion of the drug.

**Phase (in relation to Drug Development)**: Drug development is divided into phases that are determined by the main objectives of the drug development process.

- **Preclinical**: Laboratory or animal studies to show biological activity of the compound against the targeted disease, with the compound evaluated for safety and possible formulations.
- **Phase 1** : A Phase 1 clinical trial is the first step in testing a new investigational medication (or new use of a marketed drug) in humans. Phase 1 studies are mainly concerned with evaluating a drug's safety profile, including the safe dosage range. The studies also determine how the drug is absorbed and broken down by the body, what is the best way to give the drug to a patient (for example by mouth, or by injection), what side effects may be likely, and how the drug is absorbed, distributed, metabolized, and excreted as well as its duration of action. Except for drugs used to treat cancer, Phase 1 clinical trials are usually conducted in healthy individuals and are not intended to treat disease or illness. Because cancer can be such a life-threatening condition, Phase 1 trials with anti-cancer drugs are usually carried out in patients who already have the disease.
- **Phase 2** : Phase 2 clinical trials involve volunteers who have the disease or condition to be treated. These trials help physicians and researchers begin to learn more about the safety of the new drug treatment and how well the drug treats the targeted disease or condition. Several different doses of the drug may be looked at to see which dose has the desired effects. Patients are monitored for side effects and for any improvement in their illness, symptoms, or both.
- **Phase 3** : After a drug has been shown to have positive results in small groups of patients, it may be studied in a larger Phase 3 trial to confirm efficacy and identify adverse events from long-term use. A Phase 3 trial usually compares how well the study drug works compared with an inactive placebo and/or another approved medication. One group of patients may receive the new drug being tested, while another group of patients may receive the comparator drug (already-approved drug for the disease being studied), or placebo.
- **Phase 4** : Phase 4 clinical trials are sometimes called "post-marketing" trials because these studies begin after the Phase 1 – 3 study results have been given to the FDA for evaluation. These studies may be done to determine if the drug is effective against other disease states, or to test different ways of taking the drug such as tablets, time-release capsules or syrups, or to look for adverse events in larger populations over longer periods of time.

**Placebo**: An inactive substance or "sugar pill" used in comparative studies. The placebo may be used in screening or washout periods or used as a comparator to determine the efficacy of a medication.

**Primary and Secondary outcome measures**: The measures collected in a clinical trial that are intended to answer the primary and secondary objectives of the trial.

**Principles of Medical Research**

1. Lilly sponsors and supports medical research for the purpose of answering scientific questions that are important and relevant to its customers.
2. Lilly makes payments to health care providers only for legitimate, reasonable and necessary services and in amounts that are no more than the fair market value for the services performed.
3. Lilly discloses publicly all medical research results that are significant to patients, health care providers or payers—whether favorable or unfavorable to a Lilly product—in an accurate, objective and balanced manner in order for our customers to make more informed decisions about our products.

**Protocol**: A written action plan for a clinical trial. The plan states what will be done in the study and why. It outlines how many participants will take part in the study, what types of patients may take part, what tests they will receive and how often, what the treatment plan is, and the sponsor's plan to analyze the data when the study is completed.

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**Randomization**: The process of assigning trial participants to treatment or comparator groups based on chance in order to reduce potential bias. Often randomized trials will be blinded trials.

**Recruitment**: The stage of a clinical trial when human subjects or patients are being recruited to participate in the trial.

**Recruitment Advertisement**: In clinical trials, recruitment advertisements are any materials used for recruitment of study participants (e.g., letters, bulletin board notices, notices in newspapers, or on radio, television, or the Internet).

**Safety**: The practical certainty that injury will not result from exposure to a new drug under defined conditions: in other words, the high probability that injury will not result.

**Scheduled Study End Date**: For this registry, the scheduled study end date occurs when the study is completed. See Completed Study.

**Screen**: The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

**Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)**: See: Adverse Event, Serious.

**Side Effect**: See Adverse Event.

**Single-Blind Study**: A study in which the treatment group assignment is not revealed to the study participant but is known by the investigator.

**Sponsor**: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

**Statistical Significance**: A finding resulting from application of statistical procedures that a difference between a sample value and another value (either a constant or another statistic) is large enough to conclude that the two values being tested are different, that is, not due to chance or random error. The most commonly used confidence level for finding statistical significance is 0.05, meaning that there is a 5 percent or less probability that the difference observed was caused by "chance." It is important not to confuse statistical significance with clinical importance. A difference may be statistically significant and yet be so small or due to such a commonplace cause as to be of no clinical importance. Some knowledge of the area of application is needed to judge the importance of a statistically significant finding. (Source: Olson, *Statistics: Making Sense of Data* [1987]).

**Status**: Study participant recruiting status for a trial. For this registry, a trial can have one of the following statuses:

- **Not Yet Recruiting**: Study participants are not yet being enrolled.
- **Recruiting**: Study participants are currently being enrolled.
- **No Longer Recruiting**: Study participants are no longer being enrolled.
- **Completed**: Study participants are no longer being enrolled, study has had last patient visit.
- **Suspended**: The study has been stopped, but may resume at a later time
- **Terminated**: The study has been stopped, and will not resume

**Study Coordinator/Study Nurse**: The person at the investigative site who assists the investigator in the administrative coordination of the clinical trial.

**Study Drug or Trial Drug**: See Investigational Drug.

**Study Participant**: See Patient and Subject/Trial Subject.

**Study Start Date**: For this registry, a study is considered initiated when the first human subject or patient is entered in the study at any participating investigator site anywhere in the world.

**Subject/Trial Subject**: An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

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**Trial Design**: How a study is set up to collect information, or data. The design must be appropriate to answer the question being studied.

**Trial Site**: The physical location(s) where trial-related activities are actually conducted.

**Unblinding**: The act of providing visual or verbal access to the study participant, study drug treatment.

**Washout**: A period of time during a clinical study when a participant is taken off of a study drug or a medication that is not allowed during the study.

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## Terminology

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- Results in death, or
- Is life-threatening, or
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
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- Is a congenital anomaly/birth defect

**Advertisement**: In clinical trials, recruitment advertisements are any materials used for recruitment of study participants (for example, letters, bulletin board notices, and notices in newspapers, or on radio, television, or the internet).

**Biomarker**: A biomarker is a measurement of a variable related to a disease that may serve as an indicator or predictor of that disease. Biomarkers are parameters from which the presence or risk of a disease can be inferred, rather than being a measure of the disease itself.

**Blinding**: A procedure in which one or more parties to the clinical trial (i.e., the subject/patient, investigator, and/or sponsor medical personnel) are kept unaware of the treatment assignment(s) of the clinical trial participants. Used to remove potential for study bias.

**Business Partner**: Refers to major long-term business relationships that Lilly has entered with select entities for the in-licensing, out-licensing, co-development, co-marketing, or co-promotion of its products.

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**Clinical Trial / Study**: Any investigation in humans intended to discover or verify the effects of an investigational drug or new use of an already marketed drug, and/or to identify any adverse reactions to the investigational drug with the object of determining safety and/or efficacy of the studied use. The terms “clinical trial” and “clinical study” are synonymous.

**Clinical Trial Data**: All collected information arising from patients entering a clinical trial.

**Clinical Trial Material**: The testing material used in a clinical trial, including the primary study drug, comparator drugs, and placebo as specified in the study protocol. Clinical trial material includes any investigational product, including medical devices, designed for human use.

**Clinical Trial Material Package Lot Number**: An identification number associated with clinical trial material that identifies a batch of clinical trial material and from which the production and distribution history can be determined.

**Comparative Study**: A study in which a participant is randomly assigned to one of two or more treatment groups for purposes of comparing the results of the separate treatment groups.

**Comparator Drug**: An investigational or marketed drug (i.e., active control) or placebo used as a reference in a clinical trial.

**Completed Study**: For this registry, a study is considered completed on the date of the last patient visit (of the patients enrolled in that study) by an investigator authorized to conduct the study by the sponsor and the IRB/ERB.

**Confidential Information** : Information not in the public domain that is private to the study participant (such as identity or personally identifiable health information), or that is proprietary to the sponsor (such as intellectual property and some study designs and endpoints).

**Confirmatory Study** : Studies designed to support the licensing of a drug that provides the following information: establish dose response relationship; demonstrate/confirm efficacy; establish a safety profile; and provide an adequate basis for assessing the benefit/risk relationship.

**Co-operative group** : A group of physicians and/or hospitals formed to treat a large number of patients in the same way so that new treatment can be evaluated quickly.

**Core Registration Studies**: Those primary safety and efficacy studies that the relevant government health agency uses to decide whether or not to approve the investigational drug or new use of a marketed drug. These studies are usually phase 3, always well controlled, randomized, of adequate size and, whenever possible, double blind. May also be called **Pivotal** or **Confirmatory** Trials.

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**Documentation**: All records, in any form (including without limitation written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken or omitted.

**Dosing Regimen**: The expected amount of study medication prescribed per time unit and duration of dosing (for

example, 3 times/day for 7 days of therapy) as required in the study protocol.

**Double-Blind Study**: A clinical trial in which neither the investigator nor the study participant is aware of the treatment received.

**Drug**: Any recognized chemical compound that may be used on or administered to humans or animals as an aid in the diagnosis, treatment, or prevention of disease or other abnormal condition.

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**Efficacy**: The ability to produce a desired favorable effect in treating or preventing the studied disease or condition.

**Enroll**: The point at which a study participant is assigned to a study treatment in a clinical trial.

**Enter**: The act of obtaining informed consent for participation in a clinical study from participants deemed potentially eligible to participate in the clinical study.

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**Food and Drug Administration (FDA)**: A branch of the U.S. Department of Health and Human Services primarily responsible for regulating the approval and use of drugs, medical devices, cosmetics, and foods.

**Good Clinical Practice (GCP)**: A standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are respected and protected.

**Healthcare Professionals**: Medical practitioners, pharmacists, dentists, nurses, and other individuals authorized to administer or dispense pharmaceutical products.

**Hypothesis**: A scientific idea about how something works, before the idea has been tested. Scientists do experiments to test a hypothesis and see if the hypothesis is correct.

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**Indication**: The efficacy claims that are approved by the relevant government health agency for the medicine on the basis of the Core (Pivotal) Registration Studies. The indication is contained in the product label, also called prescribing information. The indications for a product may (and often do) differ by geography and country.

**Informed Consent**: A process by which a participant voluntarily confirms his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the trial relevant to the participant's decision to participate, including known and potential risks and benefits. Informed consent is documented by means of a written, signed and dated informed consent form.

**Initiated Trial**: See Study Start Date.

**Institution (Medical)**: Any public or private entity or agency, or medical or dental facility, where clinical trials are conducted.

**Institutional Review Board, or IRB:** Also known in some countries as **Ethics Review Board**, or **ERB**. This is the scientific institution that is independent of the sponsor of the clinical trial that reviews and approves the study protocol on ethical treatment grounds and ensures that each participant enrolled in the trial has given their informed consent to participate. The IRB or ERB monitors the clinical trial from inception through completion.

**Investigational Drug**: An active drug that is being studied in a clinical trial.

**Investigational New Drug Application (IND)**: After completing preclinical testing, a company files an IND with the U.S. Food and Drug Administration to begin to test the drug in humans. The IND becomes effective if FDA does not disapprove it within 30 days. The IND shows results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the investigational drug; how it is thought to work in the human body; any toxic effects found in the animal studies; and how the compound is manufactured. All clinical trials must be reviewed and approved by the Institutional Review Board (IRB) where the trials will be conducted (in Europe, the Ethics Review Board, or ERB).

**Investigator**: A health care professional responsible for the conduct of a clinical trial at a trial site and who coordinates with the study sponsor and the IRB. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

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**Labeling**: All labels and other written, printed or graphic matter on a medication or any of the medication's containers or wrappers, or that accompany the medication, such as the prescribing information. The labeling of a medication includes a description of the uses for which the medication has been approved by the government for the geography where the drug will be marketed.

**Last Patient Visit**: The "Last Patient Visit" is considered the last study visit of the last patient remaining in the trial, anywhere in the world.

**Marketed Drug**: A drug product for which marketing authorization has been granted in at least one indication in a particular country by a government health agency. Once initial marketing approval is obtained, subsequent research may be ongoing for additional indications or formulations or as part of required safety follow up.

**Methodology**: The way in which information is found or something is done. The methodology includes the methods, procedures, and techniques used to collect and analyze information.

**Multicenter Trial**: A clinical trial conducted according to a single study protocol and identical methods at more than one investigative site, and therefore, carried out by more than one investigator.

**New Drug Application (NDA)**: Following the completion of all three phases of clinical trial development, a company analyzes all of the data and files an NDA with the U.S. Food and Drug Administration if the data successfully demonstrate both safety and effectiveness. The NDA contains all the scientific information that the company has gathered on the investigational drug. NDAs typically run 100,000 pages or more and can take up to a year or longer to review by the FDA, on average. Once FDA approves an NDA, the new medicine becomes available for physicians to prescribe.

**Observational Study**: A study in which the investigator does not manipulate the use of an intervention (e.g., do not randomize patients to treatment and control groups), but only observes patients who are (and sometimes patients who are not) exposed to the intervention, and interpret the outcomes. The investigator's decisions regarding the proper treatment and care of the patient are made in the course of normal clinical practice.

**Off-label Use**: The prescribing of a medication by a physician or other healthcare provider for a use other than that which the medicine has been approved for marketing by a government health agency.

**Open-label Study**: A study in which the investigator and the study participant are aware of the drug therapy received during the study.

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**Patient**: A study participant who has the disease or condition for which the investigational product is being studied.

**Patient Files**: Hospital files, consultation records, or special patient files that are maintained and kept at the study site. In this context, also includes Phase 1 study participants, who are typically healthy volunteers without disease.

**Pharmacokinetics**: The actions of a drug in the human body over a period of time, including the absorption, distribution, metabolism, and excretion of the drug.

**Phase (in relation to Drug Development)**: Drug development is divided into phases that are determined by the main objectives of the drug development process.

- **Preclinical**: Laboratory or animal studies to show biological activity of the compound against the targeted disease, with the compound evaluated for safety and possible formulations.
- **Phase 1** : A Phase 1 clinical trial is the first step in testing a new investigational medication (or new use of a marketed drug) in humans. Phase 1 studies are mainly concerned with evaluating a drug's safety profile, including the safe dosage range. The studies also determine how the drug is absorbed and broken down by the body, what is the best way to give the drug to a patient (for example by mouth, or by injection), what side effects may be likely, and how the drug is absorbed, distributed, metabolized, and excreted as well as its duration of action. Except for drugs used to treat cancer, Phase 1 clinical trials are usually conducted in healthy individuals and are not intended to treat disease or illness. Because cancer can be such a life-threatening condition, Phase 1 trials with anti-cancer drugs are usually carried out in patients who already have the disease.
- **Phase 1b** : Phase 1b studies are usually conducted in patients diagnosed with the disease, or condition for which the study drug is intended, who demonstrate some biomarker, surrogate, or possibly clinical outcome that could be considered for "proof of concept." Proof of concept in a Phase 1b study typically confirms the hypothesis that the current prediction of biomarker, or outcome benefit is compatible with the mechanism of action.
- **Phase 1/2** : Phase 1/2 trials combine a Phase 1 and a Phase 2 trial of the same treatment into a single protocol. First the Phase 1 part of the trial is done – to determine the Maximum Tolerable Dose (MTD). Then, more patients are treated at the MTD, in the Phase 2 portion of the study, to further evaluate safety and/or efficacy.
- **Phase 2** : Phase 2 clinical trials involve volunteers who have the disease or condition to be treated. These trials help physicians and researchers begin to learn more about the safety of the new drug treatment and how well the drug treats the targeted disease or condition. Several different doses of the drug may be looked at to see which dose has the desired effects. Patients are monitored for side effects and for any improvement in their illness, symptoms, or both.
- **Phase 3** : After a drug has been shown to have positive results in small groups of patients, it may be studied in a larger Phase 3 trial to confirm efficacy and identify adverse events from long-term use. A Phase 3 trial usually compares how well the study drug works compared with an inactive placebo and/or another approved medication. One group of patients may receive the new drug being tested, while another group of patients may receive the comparator drug (already-approved drug for the disease being studied), or placebo.
- **Phase 4** : Phase 4 clinical trials are sometimes called "post-marketing" trials because these studies begin after the Phase 1 – 3 study results have been given to the FDA for evaluation. These studies may be done to determine if the drug is effective against other disease states, or to test different ways of taking the drug such as tablets, time-release capsules or syrups, or to look for adverse events in larger populations over longer periods of time.

**Pilot Study**: A Proof-of-Concept study designed to explore new hypotheses. They are not intended to be used for registration.

**Pivotal Study**: Typically a Phase 3 study which presents the data required by a regulatory agency to decide whether or not to approve a drug. A pivotal study will generally be well-controlled, randomized, of adequate size, and whenever possible, double-blind.

**Placebo**: An inactive substance or "sugar pill" used in comparative studies. The placebo may be used in screening or washout periods or used as a comparator to determine the efficacy of a medication.

**Primary and Secondary outcome measures**: The measures collected in a clinical trial that are intended to answer the primary and secondary objectives of the trial.

**Principles of Medical Research**

1. Lilly sponsors and supports medical research for the purpose of answering scientific questions that are important and relevant to its customers.

2. Lilly makes payments to health care providers only for legitimate, reasonable and necessary services and in amounts that are no more than the fair market value for the services performed.
3. Lilly discloses publicly all medical research results that are significant to patients, health care providers or payers—whether favorable or unfavorable to a Lilly product—in an accurate, objective and balanced manner in order for our customers to make more informed decisions about our products.

**Proof-of-Concept Study (POC)**: Any Phase 1b, or Phase 2 trial, regardless of sponsorship, that could generate, confirm, provide an adequate benefit-risk, or establish a dose response relationship that could be used as the basis for a decision to move forward with a registration strategy. This would include an initial indication, a supplemental indication, or a label change for a previously out-of- scope indication for a compound.
POC studies can be either Lilly-funded or managed trials, or external trials that Lilly may become aware of in a public forum. POC studies conducted using the flexibility allowed for non-registration trials can be used for internal decision-making, but positive results need to be confirmed in a registration trial.

**Protocol**: A written action plan for a clinical trial. The plan states what will be done in the study and why. It outlines how many participants will take part in the study, what types of patients may take part, what tests they will receive and how often, what the treatment plan is, and the sponsor's plan to analyze the data when the study is completed.

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**Randomization**: The process of assigning trial participants to treatment or comparator groups based on chance in order to reduce potential bias. Often randomized trials will be blinded trials.

**Recruitment**: The stage of a clinical trial when human subjects or patients are being recruited to participate in the trial.

**Recruitment Advertisement**: In clinical trials, recruitment advertisements are any materials used for recruitment of study participants (e.g., letters, bulletin board notices, notices in newspapers, or on radio, television, or the Internet).

**Safety**: The practical certainty that injury will not result from exposure to a new drug under defined conditions: in other words, the high probability that injury will not result.

**Scheduled Study End Date**: For this registry, the scheduled study end date occurs when the study is completed. See Completed Study.

**Screen**: The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

**Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)**: See: Adverse Event, Serious.

**Side Effect**: See Adverse Event.

**Single-Blind Study**: A study in which the treatment group assignment is not revealed to the study participant but is known by the investigator.

**Sponsor**: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

**Statistical Significance**: A finding resulting from application of statistical procedures that a difference between a sample value and another value (either a constant or another statistic) is large enough to conclude that the two values being tested are different, that is, not due to chance or random error. The most commonly used confidence level for finding statistical significance is 0.05, meaning that there is a 5 percent or less probability that the difference observed was caused by "chance." It is important not to confuse statistical significance with clinical importance. A difference may be statistically significant and yet be so small or due to such a commonplace cause as to be of no clinical importance. Some knowledge of the area of application is needed to judge the importance of a statistically significant finding. (Source: Olson, *Statistics: Making Sense of Data* [1987]).

**Status**: Study participant recruiting status for a trial. For this registry, a trial can have one of the following statuses:

- **Not Yet Recruiting**: Study participants are not yet being enrolled.
- **Recruiting**: Study participants are currently being enrolled.
- **No Longer Recruiting**: Study participants are no longer being enrolled.
- **Completed**: Study participants are no longer being enrolled, study has had last patient visit.
- **Suspended**: The study has been stopped, but may resume at a later time
- **Terminated**: The study has been stopped, and will not resume

**Study Coordinator/Study Nurse**: The person at the investigative site who assists the investigator in the administrative coordination of the clinical trial.

**Study Drug or Trial Drug**: See Investigational Drug.

**Study Participant**: See Patient and Subject/Trial Subject.

**Study Start Date**: For this registry, a study is considered initiated when the first human subject or patient is entered in the study at any participating investigator site anywhere in the world.

**Subject/Trial Subject**: An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

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**Trial Design**: How a study is set up to collect information, or data. The design must be appropriate to answer the question being studied.

**Trial Site**: The physical location(s) where trial-related activities are actually conducted.

**Unblinding**: The act of providing visual or verbal access to the study participant, study drug treatment.

**Washout**: A period of time during a clinical study when a participant is taken off of a study drug or a medication that is not allowed during the study.

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# *ClinicalTrials.gov* - Clinical Trial Phases

## Question: What are clinical trial phases?

## Answer:

- Clinical trials of experimental drugs proceed through four phases:
  - In **Phase I** clinical trials, researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
  - In **Phase II** clinical trials, the study drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
  - In **Phase III** studies, the study drug or treatment is given usually to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.
  - **Phase IV** studies are done after the drug or treatment has been marketed. These studies continue testing the study drug or treatment to collect information about its effect in various populations and any side effects associated with long-term use.

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*ClinicalTrials.gov* questions

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