Clinical Trials in Cystic Fibrosis:

Information for Patients

What can be the input of patients in the development of new drugs?

European Cystic Fibrosis Society

Clinical Trials Network

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1. Introduction

This brochure aims to explain how a new drug is developed and how the cystic fibrosis (CF) patients can help to make this research advance as rapidly and safely as possible.

Cystic Fibrosis (CF) is a hereditary disease. Relentless lung infections and poor digestion are the main symptoms. With modern medicines, survival into the middle age, even after a diagnosis in childhood, is now common, provided that certain conditions are met. Still the disease is life shortening. As the patient's health declines, the complexity and the cost of the treatment increase and the quality of life decreases. The disease occurs all over the world in males and females and is the most common life-threatening genetically inherited disease affecting Caucasians. Still it is classified as a rare (or "orphan") disease. Across 27 EU countries, the prevalence is 0.74 per 10.000 and around 30.000 CF patients are registered in 35 European countries.

The genetic cause of the disease has been known for 20 years and consists of errors on both copies of the gene coding for the CFTR protein. Cystic fibrosis is indeed an **autosomal recessive disease**. This means that it occurs in both sexes ("autosomal" means the gene does not lie on the sex chromosomes). "Recessive" means that only people with an error in both copies of the CFTR gene suffer from the disease. Persons with CF thus inherited an abnormal CFTR gene from both parents. The parents are healthy, they only carry one abnormal copy of the CFTR gene. They are called carriers. When both partners carry an abnormal copy of a CFTR gene, with every pregnancy there is a 1/4 chance that the fetus will be affected.

In CF, there is an abnormality in the genetic code, and the protein called CFTR is not able to function properly.

The CFTR protein allows the transport of salt in various organs. In the airways, when the CFTR protein does not function properly, inhaled bacteria and other disease causing organisms are poorly eliminated and cause chronic airway infection. In the digestive system, abnormal salt transport results in impaired secretion of digestive enzymes and problems in digestion and underweight occur.

Knowledge on how the error in the gene leads to absence or dysfunction of the protein, opened up a new era of research. Several small chemical compounds have been identified that are able to overcome the basic defect of CF in cell cultures. These new strategies are now being evaluated in patients. In addition, also research to improve the treatment of lung infection and digestion problems remains important.

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For a rare disease like CF, drug companies know that the potential market for selling drugs is relatively small. Luckily, **laws have been written to encourage research into rare diseases and possible cures.**

In 2008, a milestone has been reached in our fight against CF. For the first time ever drugs aimed at correcting the cause of the disease, called 'disease modifying drugs' were shown to be non toxic, well tolerated and to have some efficacy in small and moderate size studies. These drugs, but also other new drugs that slow disease progression, now need to be tested on large numbers of patients.

2. Types of drugs

- **CFTR modulators:** These therapies aim to correct the dysfunction of the defective CFTR protein. There are different possible modes of action, that are related to specific subsets of genetic mutations in the CFTR gene. These therapies are promising as they work on the basic defect (so called "disease modifying drugs"). This means they aim to correct the cause of CF and not just the downstream consequences like lung infections. Examples that are currently being studied in patients are VX-770 and VX-809 (Vertex) and Ataluren® (PTC Therapeutics).

- **Restoration of airway surface liquid:** These therapies target proteins other than CFTR that have a similar function (movement of salts in or out of cells). This can lead to better hydration and clearance of the airway mucus.

- **Mucus alteration:** Well known by all of you is rhDNase or Pulmozyme®. RhDNase destroys certain parts of the mucus so it becomes less sticky. This drug has become available after many years of testing in large groups of CF patients. Hypertonic saline is also available as drug and several other products are in the clinical trial phase.

- **Anti-inflammatory:** These drugs aim to calm down the inflammation process in the lungs, using several methods. An example product is Ibuprofen. Several other molecules are being tested in clinical trials.

- **Anti-infective:** These drugs are antibiotics that attack the micro-organisms that are causing acute and chronic lung infections. Example products are Tobramycin (TOBI®) and Azithromycin. Other products are being tested in

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clinical trials, mostly antibiotics well known to be active against Pseudomonas aeruginosa and formulated for aerosols. As organisms such as Pseudomonas aeruginosa can become resistant, it is important to have different types of antibiotics available.

- **Nutrition:** This involves supplements like vitamins, but also the enzymes like Creon®, that help to digest the food.

- **Other treatment strategies:** Gene therapy is still in the early development phase. The challenges are to find a way to introduce into the airways normal copies of the gene that is defective in CF and to obtain gene expression (conversion of the information encoded in the gene into a correct CFTR protein).

3. What is a clinical trial, what are the aims?

A clinical trial is a study in human volunteers to test if new potential treatments are safe and effective.

"Effective" means the drug works better than the currently used treatment and helps the patient feel better

No drug is completely free from side effects, but a drug is considered safe if the benefits from taking it outweigh the possible negative side effects. In order to guarantee that an intended clinical trial is justified there are various regulatory agencies in each country. Their job is to review the safety and efficacy results of the preclinical studies and check that the purpose and the procedures of the clinical trial are justified and acceptable. Their approval is mandatory before a clinical trial can begin. One example is the Ethics Committee which exists in each country and which is dedicated to review the clinical trial as regards the rights and well-being of patients participating in the trial (see below).

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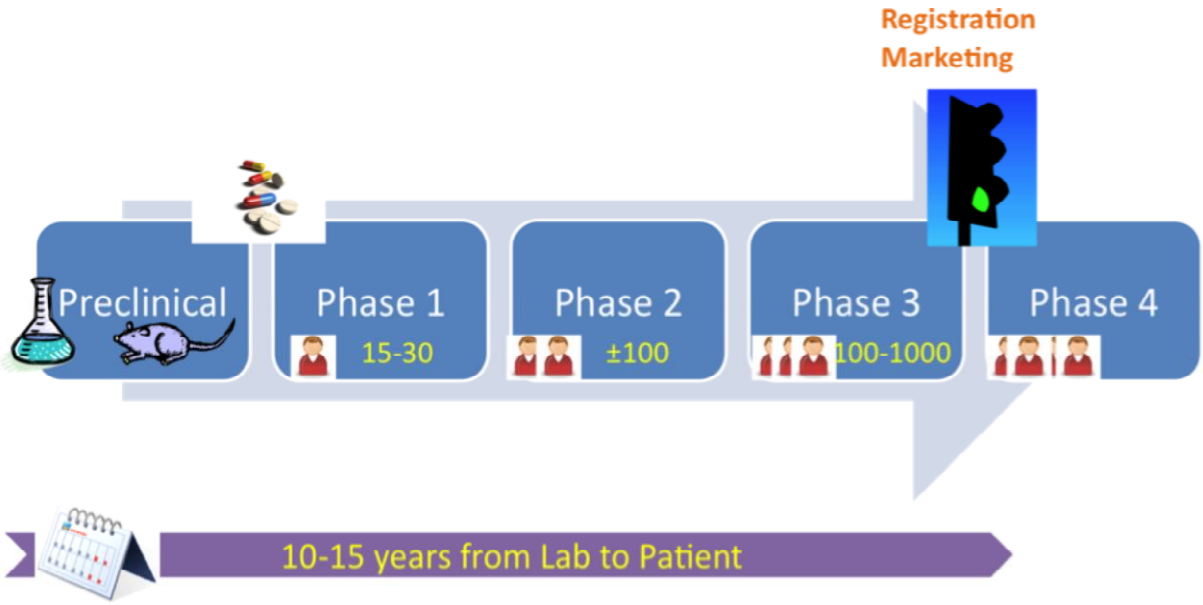
4. What is the process for development of a new drug?



When a new drug is being developed, the first studies are performed in what is called a **preclinical phase**. It means that the drug is tested extensively in the lab, in cells and in animal studies. If these studies show a possible benefit without toxicity, it can enter the subsequent clinical phases in which it is tested in clinical trials in humans.

After the preclinical phase, there are 3 consecutive phases of trials needed before the drug can be approved by the authorities and consequently marketed.

1 In **Phase 1 trials**, researchers test an experimental drug or treatment in a small group of people (around 20, usually healthy volunteers) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. the treatment period per patient is only a couple of days to a couple of weeks.

2 In **Phase 2 trials**, the experimental study drug or treatment is given to a larger group of patients with the disease, here CF (20-400) to see how well it works and to further evaluate its safety.
Treatment period per patient is around 1 to 3 months.

3 In **Phase 3 trials**, more patients are involved (100-1000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments (if it gives better results, it may become the new standard treatment), and

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collect information that will allow the experimental drug or treatment to be used safely.
Treatment period per patient can range from around 1 month to more than 1 year.

It is only after these successful Phase 3 trials that the drug can be approved by the authorities and consequently marketed.

 **The drug is then in Phase 4** in which information on long term risks and benefits is collected from all patients prescribed the drug.

It can take 10-15 years before a new drug that is discovered in the lab is ready to be prescribed to patients. Only a small percentage of tested candidate drugs will reach the end of the process. This makes drug development very expensive for companies, especially because cystic fibrosis is a ”rare disease” so the market to sell these drugs (also called “orphan drugs”) will be relatively small. Luckily the European Community created special regulations, so that there are still advantages for companies to work on the development of orphan drugs. If you like to read more about this subject you can visit the Eurordis website http://www.eurordis.org

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5. Why are children also involved in clinical trials?

- CF is a disease **affecting children from birth**. Follow-up and treatment aim to prevent disease progression from very early age.
- **"A child is not a small adult"**: There are age specific metabolic differences that make children react differently to the same drug. Therefore it is not safe or effective to simply adapt the dose for a drug that is recommended to an adult. Moreover, a different formulation is often needed for smaller children (for example syrup versus pills).
- Therefore, according to **European regulations**, pharmaceutical companies have to present a "pediatric investigation plan" (PIP) when testing a new drug. This is a development plan aimed at ensuring that the necessary data are obtained through studies in children, when it is safe to do so, to support the authorisation of the medicine for children. You can find more information on this topic on the website of the EMA (European Medicines Agency") http://www.ema.europa.eu

Clinical trials in CF also involve (small) children. Of course this is never done without informing the parents and obtaining their approval (informed consent). In addition, older children and teenagers can be asked to provide their agreement to participate. This is called "assent".

6. How is voluntary participation guaranteed?

Information and Informed Consent

Informed consent is the process of learning the key facts about a clinical trial before deciding whether or not to participate. To help someone decide whether or not to participate, the doctors and nurses involved in the trial explain the details of the study. Then the research team provides an informed consent document that includes details about the study, such as its purpose, duration, required procedures, and key contacts. Risks and potential benefits are explained in the informed consent document. The participant then decides whether or not to sign the document.

Informed consent is not a contract, and the participant may withdraw from the trial at any time. Informed consent makes certain that participants can ask questions and get answers before, during and after the trial. You can discuss the Informed Consent Form with family or friends and bring somebody to the meeting.

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A subject that declines to participate in the study will not have a risk of compromising present or future medical care and will not suffer a penalty or loss of benefits to which they are otherwise entitled.

Every human subject has the right to understand the nature, and the risks and benefits of the research, and to agree or not agree to participate.

7. How is safety monitored?

The sponsor and the investigators participating in a clinical trial bear the final responsibility for the conduct of the trial. However there are several regulations and committees that help to monitor this:

a. Regulations for clinical trials

There are specific rules set-up, to make sure that people who agree to be in studies are treated as safely as possible. In Europe, this is one of the tasks of the European Medicines Agency (EMA). In US, this is handled by the Food And Drugs Administration (FDA).

These rules are called: **"Good Clinical Practice"** or "GCP".

The above mentioned institutions can perform inspections of clinical trial study locations to check if the GCP rules are followed and to protect the rights of participants. Also the quality and integrity of the data is verified.

b. Institutional Review Board (IRB)

The Institutional Review Board is an independent body charged with **protecting the rights, safety and welfare** of people involved in research. All institutions that are involved with research (places such as colleges and hospitals), must appoint such a committee or board. The members are both medical/scientific and non-

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medical/non-scientific professionals (for example an ethics specialist). An IRB has the authority to approve, require modifications, or disapprove research.

IRB is also known as:

- Independent Ethics Committee (IEC)
- Ethics Review Board (ERB)
- Ethics Committee (EC)

The chief responsibilities of the IRB are:

1. Approval/Permission for the conduct of clinical trials
2. Review of the study progress
3. Make sure all the rules are followed (Regulatory Compliance)

c. Data Safety Monitoring Board

The "Data Safety Monitoring Board" or "DSMB" is an independent committee that reviews data while a clinical trial is in progress to ensure that participants are not exposed to undue risk. A DSMB may recommend that a trial be stopped if there are safety concerns or if the trial objectives have been achieved.

Sometimes it is also called a "Data Monitoring Committee" or "DMC". Not all clinical trials require a DSMB or DMC.

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8. What will be asked of me when I am participating in a trial?

The complete **visit schedule and associated procedures** will be explained to you by the study team. This will be different for every study. The duration of the study can vary from a couple of weeks to more than a year.

Of course it will be really important to **take the study treatment** and your other medications according to the instructions provided. This is called "compliance". For some studies, there can be lifestyle and/or dietary restrictions, for example contraception requirements or restriction in the use of alcohol or tobacco.

You are followed up at different **"study visits"**. If possible some of these visits will be combined with your standard check-up visits at the hospital. Sometimes visits are done at home or even by telephone. For some more complex studies, overnight stays at the hospital might be required.

2 important visits are the screening visit and the randomisation visit:

Screening visit: This is the first visit of the trial. This visit cannot begin before the informed consent form is signed. The purpose of this visit is to check if a candidate participant is meeting all the inclusion and exclusion criteria of a specific protocol (For example if the lung function results are within a certain interval). Baseline samples such as blood, urine or sputum may also be taken. If all conditions are met, the candidate can continue to participate in the study. The purpose of these inclusion and exclusion criteria is to identify appropriate participants and keep them safe.

Randomisation visit: randomisation means it is decided by chance (=randomly) what kind of study treatment the patient will receive (in case two treatments are compared to each other); or it is randomly decided if he/she will receive active drug or placebo (in a placebo controlled trial). There are also other designs possible. At or just after this visit, the patient starts taking the study treatment.

A placebo is an inactive pill, liquid, or powder that has no treatment value. In clinical trials, experimental treatments are sometimes compared with placebos to assess the experimental treatment's effectiveness. This design is only used if it has been evaluated as ethically acceptable for that specific study.
Most of the studies are double-blind. This means that neither the patient, nor the doctor knows what treatment the patient is using, or if a patient is on placebo drug. The blinding can only be broken in very specific conditions.

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Example procedures:

Common:

Physical examination
Spirometry / other pulmonary function tests
Electrocardiogram
Blood and urine samples
Sputum sample
Questionnaire
…

Less common:

Specific tests such as Nasal Potential Difference (NPD)
Audiogram
Sweat test
Stool collection
…

9. What should people consider before participating in a trial?

People should know as much as possible about the clinical trial and feel comfortable asking the members of the health care team questions about it.

The following questions might be helpful as a guideline. Some of the answers to these questions are found in the informed consent document.

- *What is the purpose of the study?*
- *Who is going to be in the study?*
- *Why do researchers believe the experimental treatment being tested may be effective? Has it been tested before?*
- *What kind of tests and experimental treatments are involved?*
- *How do the possible risks, side effects, and benefits in the study compare with my current treatment?*
- *How might this trial affect my daily life?*
- *How long will the trial last?*
- *Will hospitalisation be required?*
- *Who will pay for the experimental treatment?*
- *Will I be reimbursed for other expenses?*
- *What type of long-term follow up care is part of this study?*
- *How will I know that the experimental treatment is working? Will results of the trials be provided to me?*
- *Who will be in charge of my care?*

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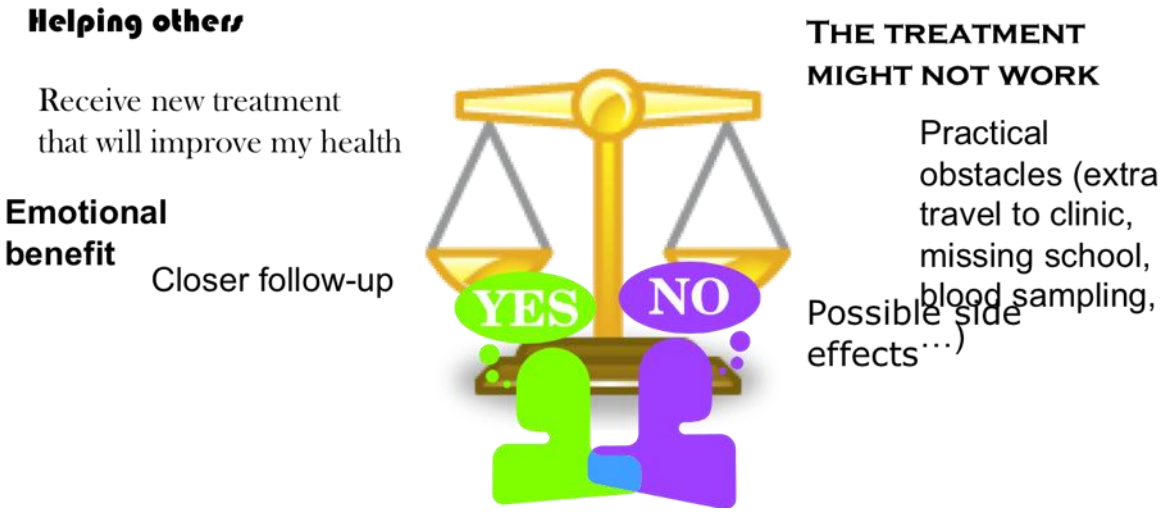
There are several factors that can motivate or discourage patients to participate in clinical trials:



10. What is the role of European Cystic Fibrosis Society – Clinical Trials Network (ECFS-CTN)

For a rare disease such as CF, it is important that **countries work together** as much as possible. Also there is need for a close cooperation between patients, patient organisations, pharmaceutical industry and academic research institutions.

When trying to **standardize new or existing working methods** (for example to measure lung function or to perform a sweat test), it is important to have an international dialogue. If everybody works the same way, there is less variation in results, which means that less patients have to participate in a clinical trial to prove the same effect.

To promote such cooperation, the European Cystic Fibrosis Society (ECFS) which is a learned European Society dedicated to CF, took the initiative to setup a "Clinical Trials Network" (CTN). Currently this network combines CF specialists from 18 centres in 8 countries, and will expand to more countries and sites in 2012.

An important task of the ECFS-CTN is the **review of new study protocols** by a team of experts. They look at the scientific quality, but also at the feasibility for the patient and the therapeutic importance of the tested drug. Centres that are part of the CTN will only conduct trials that have been approved by this review system.

The aim of the CTN is to bring new medicines faster to the patients by promoting high quality research in different ways.

Please find more information on the CTN activities at http://www.ecfs.eu/ctn/.

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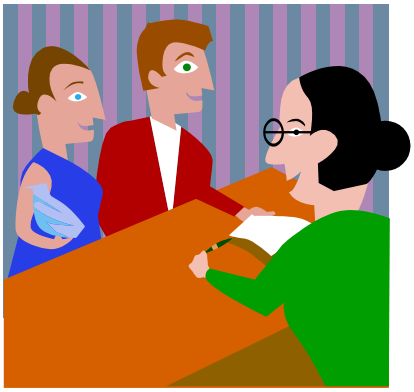
11. What do I have to do if I want to participate in a clinical trial? How can I find out about upcoming and ongoing clinical trials?

To bring medicines to the patients faster, it is critical that clinical trials be conducted and that patients participate in these trials. However, even if you want to volunteer for participation in a study, you may still be excluded based on the inclusion/ exclusion criteria of a given protocol, and/or the number of participants needed by the researchers. If you want to participate in clinical trials, you should first of all ask the Doctor that is treating you or another member of your **CF care team**. They will be the best people to help you with this question. Because they know your background, they will be able to advise you in which clinical trial you may participate and to tell if you match the inclusion criteria of one or more studies that are running in your centre.



- **National Patient Organisations:** some national CF associations have a clinical trials section on their website that is showing which trials are going on in the country.

- **Clinicaltrials.gov** (http://www.clinicaltrials.gov/) is a service of the U.S. National Institutes for Health. It is an online database of clinical trials conducted in the United States and around the world. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers for more details. This information should be used in conjunction with advice from health care professionals. There is a search tool where you can type one more keywords (for example “cystic fibrosis and pediatric”).

- **ECFS-CTN Website (**http://www.ecfs.eu/ctn/clinical-trials**)**
  The clinical trials section of the ECFS-CTN website provides an overview of studies that are ongoing in centres that are part of the network. If available, results are posted for trials that are finished.

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12. Glossary

- **(Clinical) Investigator:** A medical researcher who carries out a clinical trial or another type of clinical research.
- **Control group:** In many clinical trials, one group of patients will be given an experimental drug or treatment, while the control group is given either a standard treatment for the illness or a placebo. This way the new treatment's effectiveness can be assessed.
- **Data Safety Monitoring Board (DSMB):** An independent committee that reviews data while a clinical trial is in progress to ensure that participants are not exposed to undue risk. A DSMB may recommend that a trial be stopped if there are safety concerns or if the trial objectives have been achieved.
- **Double blind trial:** A clinical trial design in which neither the participating individuals nor the study staff knows which participants are receiving the experimental drug and which are receiving a placebo (or another therapy). Double-blind trials are thought to produce objective results, since the expectations of the doctor and the participant about the experimental drug do not affect the outcome
- **Eligibility criteria / inclusion-exclusion:** the criteria determining whether a person may or may not be allowed to enter a clinical trial. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. It is important to note that inclusion and exclusion criteria are not used to reject people personally, but rather to identify appropriate participants and keep them safe.
- **Enrollment:** Number of subjects in the trial.
- **Good Clinical Practice (GCP):** an international quality standard that is provided by the International Conference on Harmonisation (ICH), an international body that defines standards, which governments can transpose into regulations for clinical trials involving human subjects.
- **Open-label trial:** Clinical trial in which the researchers and the study participants know the treatment drug they are taking.
- **Outcome measures / endpoints:** Before a clinical trial begins, researchers must determine what criteria of efficacy they will monitor to measure the effect of the study treatment (or other intervention). For example in a phase 3 CF study the primary endpoint is often the lung function test result (FEV_1).
- **Pharmacokinetics (PK):** This is the analysis of how the body absorbs, distributes, breaks down, and eliminates a drug. This is mostly measured by taking a series of blood and/or urine samples and measuring the amount of drug or its metabolites in function of time.

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- **Placebo:** 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. In some studies, the participants in the control group will receive a placebo instead of an active drug or experimental treatment.
- **Protocol:** Clinical trials are conducted according to a plan called a protocol. The protocol describes what types of patients may enter the study, schedules of tests and procedures, drugs, dosages, and length of study, as well as the outcomes that will be measured.
- **Randomisation visit:** randomisation means it is decided by chance (=randomly) what kind of study treatment the patient will receive (in case two treatments are compared to each other). Or it is randomly decided if he/she will receive active drug or placebo (in a placebo controlled trial). There are also other possible designs. At or just after this visit, the patient starts taking the study treatment.
- **Randomised study:** A study in which participants are randomly (i.e., by chance) assigned to one of two or more treatment arms of a clinical trial. Occasionally placebos are utilised.
- **Screen failure**: a subject not meeting the protocol inclusion / exclusion criteria after the screening visit has taken place.
- **Screening visit:** This is the first visit of the trial, where it is checked if a candidate participant is meeting all the inclusion and exclusion criteria of a specific protocol.
- **Sponsor:** Individual, company, institution or organization responsible for initiation, management and financing of a study.

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13.References and additional information:

Clincaltrials.gov "understanding clinical trials": http://clinicaltrials.gov/ct2/info/understand

National Cancer Institute "introduction to clinical trials":
http://www.cancer.gov/clinicaltrials/learning

CFF-TDN website (Therapeutic Development Network of the Cystic Fibrosis Foundation in US): http://www.cff.org/research/TDN/

ECFS-CTN website: http://www.ecfs.eu/ctn/

US Food and Drug administration (FDA): http://www.fda.gov/

European Medicines Agency (EMA): http://www.ema.europa.eu/

ECORN: Expert advice on Cystic Fibrosis: http://ecorn-cf.eu/

Patient Partner project and European Network for Patients Partnering in Clinical research (ENPCR): http://www.patientpartner-europe.eu/

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14. List of websites for some national CF associations (patient organisations) in Europe:

Worldwide: Cystic Fibrosis Worldwide - http://www.cfww.org/

Europe: Cystic Fibrosis Europe - http://www.cfeurope.org/

- **Austria**

  Cystischen Fibrose Hilfe Österreich - http://www.cf-austria.at/cms/

- **Belgium**

  Belgische Vereniging Voor Strijd Tegen Mucoviscidose - Site in Flemish: http://nl.muco.be/

  Association Belge de Lutte contre la Mucovisidose - Site in French: http://fr.muco.be/

- **Bulgaria**

  Асоциация Муковисцидоза (Association Mucoviscidosis) - http://www.lifewithcf.org/

- **Czech Republic**

  Klub nemocných Cystickou Fibrózou - http://www.cfklub.cz/

- **Denmark**

  Danish Cystic Fibrosis Association - http://www.cystiskfibrose.dk/default.html

- **France**

  Association Vaincre la Mucoviscidose - http://www.vaincrelamuco.org/

- **Germany**

  Mukoviszidose e.V. - http://muko.info/

  CF-Selbsthilfe Koeln e.V - http://www.cf-selbsthilfe-koeln.de/

- **Greece**

  Hellenic C.F. Association - http://www.hcfa.gr/

- **Italy**

  Italian Cystic Fibrosis Research Foundation - http://www.fibrosicisticaricerca.it/

  Lega Italiana Fibrosi Cistica - http://www.fibrosicistica.it/

- **Ireland**

  The Cystic Fibrosis Association of Ireland - http://www.cfireland.ie/

- **Israel**

  Cystic Fibrosis Foundation of Israel - http://www.cff.org.il/

- **Netherlands**

  Nederlandse Cystic Fibrosis Stichting - http://www.ncfs.nl/

- **Norway**

  Norsk Forening For Cystisk Fibrose - http://www.cfnorge.no/

- **Poland**

  Polish Society Against CF - http://www.ptwm.org.pl/

- **Portugal**

  Associação Portuguesa de Fibrose Quística - http://www.apfq.pt/

- **Slovenia**

  Cystic Fibrosis Association Slovenia - http://www.drustvocf.si/
- **Spain**

  Federación Española contra la Fibrosis Quística - http://www.fibrosisquistica.org/
- **Sweden**

  Riksförborbundet Cystisk Fibros - http://www.rfcf.se/
- **Switzerland**

  Schweizerische Gesellschaft für Cystische Fibrose (CFCH) - http://www.cfch.ch/
- **Russia**

  Russian Cystic Fibrosis Site - http://www.mucoviscidos.ru/
- **UK**

  Cystic Fibrosis Trust - http://www.cftrust.org.uk/

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