Adherence

In medicine, adherence describes the degree to which a patient correctly follows medical advice. Poor adherence is often associated with patients not following prescribed medicines and treatment regimes. Non-adherence or poor adherence has been reported as a major problem in medical practice and can also affect the outcomes of a clinical trial. Poor adherence, or failure to follow treatment instructions, may be attributed to a number of reasons such as poor communication, forgetfulness, or unpleasant side-effects.

Efforts to improve adherence in clinical practice have included simplifying medication packaging, providing medication reminders, improving patient education, and limiting the number of medications prescribed simultaneously. Various measures of adherence are used in clinical trials, for instance: the assessment of pharmacological response, electronic diaries, residual tablet count, devices to monitor tablet removal from containers, testing for medicine in blood or urine, or the use of pharmacological markers/indicators.

Adjuvant

An adjuvant is a substance (pharmacological and/or immunological) that modifies the effect of other substances or medicines. Immunological adjuvants may be added to vaccines to boost the immune response. Adjuvant therapy or care is therapy that is given in addition to the main or initial therapy to maximise its effectiveness. For example, radiotherapy is commonly given as adjuvant treatment after surgery for breast or other cancers.

Advanced therapy medicinal products

Advanced therapy medicinal products (ATMP) are new medical products for human use based on genes (gene therapy), cells (cell therapy), or tissues (tissue engineering). They have huge potential and open the way for new treatments of a number of diseases or injuries, such as skin in burns victims, Alzheimers, cancer, or muscular dystrophy.

Adverse drug reaction

A response to a medicinal product which is harmful and unintended. Response in this context means that a causal relationship between the medicinal product and an adverse event is at least a reasonable possibility.

Adapted from the Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 3) 2014.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf

Adverse event

Any untoward (not favourable) medical occurrence in a patient, or clinical trial participant receiving a medicine, and which does **not** necessarily have a causal relationship with this treatment.

Adverse events can therefore be: any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease **temporally associated with the use of a medicine**, whether or not considered related to the medicine.

Adverse reaction

An adverse reaction, is any adverse event or experience related to a medicine for **which a reasonable causal relationship with the medicines use is suspected**. This is synonymous with adverse drug reaction (ADR).

Allogeneic cells

Allogeneic cells are cells obtained from a donor, such as bone marrow or umbilical cord blood.

Antibody

An antibody (AB), also known as an immunoglobin, is a protein produced by the bodys immune system when it detects harmful substances (called antigens). Antigens can be molecules from microorganisms (bacteria, fungi, parasites, and viruses), or chemicals (insect venom). Antibodies recognise and latch onto antigens in order to neutralise them.

Antigen

The part of a pathogen that stimulates a response from the immune system.

Arm

In clinical research this refers to any of the treatment groups in a randomised trial. Many randomised trials have two "arms" or groups, but some may have three or even more.

Autologous

Autologous tissue or cells are tissue or cells derived from the same individual. For example, skin transferred from one part of the body to another is autologous tissue; in advanced therapies, stem cells are removed, stored, and later given back to the same person. Autologous transplants are used to treat a number of different blood cancers. Autologous stem cell transplantation is distinguished from allogeneic stem cell transplantation, where the donor and the recipient of the transplanted stem cells are different people.

Benefit

Benefit is a positive outcome (such as the relief of symptoms, cure, or prevention) from using a treatment or taking part in a study. The benefits of taking part in research may include helping others by participating in medical research, close monitoring by health professionals and experts, or getting access to an effective treatment before it is made available to the wider patient population.

Benefit-risk assessment

In medicines R&D, benefit-risk assessment is the continuous examination of the favourable and unfavourable results of a specific treatment to determine whether its benefits outweigh its risks in a -specific condition. It takes into account the evidence on safety and efficacy, as well as other factors like the nature and severity of the condition the medicine is intended to treat or prevent.

Best supportive care

Best supportive care (BSC) is the treatment of choice when a cure is not achievable with existing treatments. It involves the management of disease-related symptoms.

Bias

In clinical trails, bias is the systematic deviation from true values of treatment effect through the intentional or unintentional adjustment of results. Bias can result from aspects of trial design, the way a trial is carried, or the way the results are analysed or evaluated.

Bias can be "operational" when it arises because of the way a trial is carried out; or "statistical" when it arises because of trial design or the way results are analysed or evaluated

For example, poor trial design might mean that participants at lower risk of experiencing a symptom are placed in one treatment arm as opposed to another treatment arm. Excluding data from certain participants because of knowledge of their outcomes would also cause bias in a trial.

The most important design techniques for avoiding bias in clinical trials are blinding and randomisation. The potential effect of bias should also be taken into account during statistical analysis of trial data.

Big data

Big data in the health sector is the combination and analysis of very large and diverse sets of data, such as non-health and health data, ongoing generation of information about the real-world use of medicines, patient-generated data from social media, and wearable devices.

Biobank

A biobank is a large, organised collection of samples, usually human, used for research. Biobanks catalogue and store samples using genetic, clinical, and other characteristics such as age, gender, blood type, and ethnicity. Some samples are also categorised according to environmental factors, such as whether the donor had been exposed to some substance that can affect health. Biobanks play a crucial role in biomedical research, such as in genomics and personalised medicine. Researchers access biobanks when they need samples with similar characteristics for their research studies.

Bioequivalence

Bioequivalence means that the identical active pharmaceutical ingredient of two medicines have the same rate and extent of absorption. The medicines produce the same effect at the required target. For example, a receptor in the brain can be a target for a medicine. Bioequivalence is often used to compare an original and generic version of a medicine, or two different formulations (for instance, tablet or oral suspension) of the same medicine.

Bioethics

Bioethics is the application of ethics to the fields of medicine, biomedical research and health policy. It has become an important area of enquiry as advances are made especially in genetic medicine and reproduction. The ethical aspects of research and policy are often included under the title "ELSI", which stands for "ethical, legal and social issues".

Biologic medicine

A biologic medicine is any medicinal product manufactured in, extracted from, or synthesised in part from biological sources. Biologics can be composed of sugars, proteins, or nucleic acids; they may be complex combinations of sugars, proteins, or nucleic acids; or they may be living cells or tissues. Some of the oldest forms of biologics are extracted from the bodies of animals and other humans such as whole blood and blood components.

Some traditional biologics are now produced in the laboratory rather than from living tissue for example, tissue for transplants, antibodies for passive immunisation, and insulation. Different from chemically synthesized pharmaceuticals, they include vaccines, blood or blood components, gene therapies, and living cells used in cell therapy.

Biomarker

A biological marker is something that can be measured which points to the presence of a disease, a physiological change, response to a treatment, or a psychological condition. For example, glucose levels are used as a biomarker in managing diabetes, and brain images can provide information about the progression of multiple sclerosis.

Biomarkers are used in many scientific fields. They are used in different ways at different stages of medicines development, including in some cases as a surrogate endpoint to indicate and measure the effect of interventions, such as medicines, in trials.

For example, haemoglobin levels have been used in Phase III trials to support development of therapies for Type 1 Gaucher disease (a rare disease that affects multiple organ systems and shortens life expectancy, but which can take years to show changes in clinical symptoms).

Biosimilar Medicine

A biosimilar medicine is a biological medicine which is similar to another biological medicine that has already been authorised for use. Biosimilar medicines are commonly known as biological generic medicines. The existing biological medicine is known as the reference medicinal product. Biosimilars may only be marketed after the patent for the reference medicinal product has expired, although they may be developed earlier. A biosimilar medicine and its reference medicinal product are expected to have the same safety and efficacy profile.

Biosimilar medicines are developed to have the same mechanism of action, and to treat the same diseases as the reference medicinal product. Standards of the EU Good Manufacturing Practice (GMP) apply to the manufacture of biosimilar medicines in the same way as for any other biological medicinal product. Biosimilar medicines may offer a less costly alternative to existing biological medicinal products that have lost their exclusivity rights.

Biotechnology

Any technological application of living systems, biological processes or organisms, to develop or make useful products or new technologies.

Blinding

Blinding is a way of making sure that the people involved in a research study, such as the participants in clinical trials, do not know which trial arm they are assigned to. For example, in a trial with one treatment arm and one placebo arm, blinding means that the participants do not know if they are receiving the treatment or the placebo.

Blinding is used to remove bias that can be caused intentionally or unintentionally if participants or the research team are aware of which trial group participants are in.

Sometimes the term single-blind is used to describe studies where the participants are unaware of which arm they are in, but the research team does know. In a double-blind trial, both the research team and participants do not know which participant is assigned to which arm.

A blind trial is the opposite of an open or open-label trial.

Branded Medicines

Branded medicines are medicines which have a name given to them by a company for the purpose of advertising. The names of branded medicines are different from the International Nonproprietary Name (INN), also known as the generic name. Branded medicines may be the original medicine developed by a company or several companies may make the same generic medicine, to which each company gives its own brand name.

Budget impact

Costs within a particular timeframe and related to a particular healthcare budget rather than a countrys overall budget. This assumes robust data on epidemiology and treatment patterns, along with assumptions of uptake and displacement of current treatments.

Candidate drug

In the medicines development process, this is the compound among several (compounds), which meets criteria in efficacy and safety in order to be used in clinical trials with humans. Broad information on the mechanism of action and pharmacology has to be available for a candidate drug.

Case Control Studies

A case control study is one that compares two groups retrospectively.

For example, people who developed a disease might be compared with a group of people who have not. The researcher will look at whether there is any difference in the two groups in their previous exposure to possible risk factors. This kind of study is useful when studying risk factors for rare diseases, and is often used to create new hypotheses which can then be tested.

For example, there are fewer than 300 confirmed cases of new-variant Creutzfeldt-Jakob disease (CJD). A cohort study that follows healthy people over time to see what risk factors might lead to the development of the disease would need to recruit a huge number of people in order for just one to develop symptoms (around 200,000). It would also take a very long time, because the period between infection and the appearance of symptoms is thought to be between 10 and 30 years. A much better approach in this case is to carry out a case control study, beginning with people who have already been diagnosed with new-variant CJD, and comparing their past exposure to possible risk factors with a group of people who do not have the disease.

Case report form

A case report form is a paper or electronic data entry form used in clinical trials. It is used by sites taking part in clinical trials (such as hospitals) to collect data about each trial participant. All the data on each individual taking part in a clinical trial, including information on adverse events, are held in the case report form.

A case report form is developed specifically for each clinical trial so that all the data needed to answer the research question is captured. The organisation running the trial is responsible for designing a case report form in line with the protocol of the trial. They must also monitor and audit the data that is collected to ensure it is complete and accurate.

Personal data such as, the patients names, medical record numbers, and any other identifying information are usually not disclosed in the CRFs. Each patient is instead given a unique identifier.

Centralised procedure

The centralised procedure is a process for obtaining marketing authorisation for a medicine in the EU. The European Medicines Agency (EMA) oversees the centralised authorisation procedure for human and veterinary medicines. This procedure results in a single marketing authorisation, granted by the European Commission, which allows a medicine to be marketed in all EEA (European Economic Area) countries (EU member states and the three EEA EFTA States: Iceland, Liechtenstein, and Norway).

Chemotherapy

Chemotherapy is a type of cancer treatment that uses medicines to destroy cancer cells. Chemotherapy is used along with surgery, radiation therapy, or biological therapy. It works by stopping or slowing the rapidly growing cancer cells. However, chemotherapy can also harm healthy cells that divide quickly, such as those that line the mouth and intestines. Due to the effect these medicines have on healthy cells, serious or severe side effects are common.

Chronic Condition

A chronic condition is a long-lasting disease that can be controlled but not cured. The term chronic is usually applied when the course of the disease lasts for more than three months.

Common chronic diseases include asthma, chronic obstructive pulmonary disease (COPD), cancer, and diabetes. In certain diseases or conditions, prevention is effective in reducing the possible development of the condition or its effect. Early diagnosis and timely treatment can help to reduce serious effects of the condition.

Class effect

Class effect refers to the similar outcomes, therapeutic effects and similar adverse effects of two or more medicines. All products within a class are assumed to be closely related in three concepts: a similar chemical structure, mechanism of action, and pharmacological effects.

Clinical effectiveness

As a component of a dossier submitted for HTA assessment, clinical effectiveness is a measure of how well a particular treatment works in the practice of medicine. It depends on the application of the best knowledge derived from research, clinical experience, and patient preferences.

Clinical efficacy

In medicine, clinical efficacy indicates a positive therapeutic effect. If efficacy is established, an intervention is likely to be at least as good as other available interventions to which it will have been compared. When talking in terms of efficacy versus effectiveness, efficacy measures how well a treatment works in clinical trials or laboratory studies. Effectiveness, on the other hand, relates to how well a treatment works in the practice of medicine.

Clinical phase

The clinical phase of medicines development is the one involving humans, and is different from the non-clinical or pre-clinical phase in which studies are performed in labs or in animals (such as for pharmacology/toxicology analysis). Clinical studies are conducted in four steps, called "phases" - each designed to answer separate research questions.

Clinical Practice

Clinical practice is the treatment and management of patients by healthcare professionals supported by clinical-based evidence. There are clinical practice guidelines that have been designed to assist health professionals and patients in decisions about appropriate health care for specific circumstances.

Clinical study

A clinical study is a scientific investigation in which participants receive a health-related intervention, such as a medicine, in order to learn about (discover or verify) how it works and interacts with the body (clinical, pharmacological, pharmacodynamic, and pharmacokinetic effects), or to identify any adverse reaction in order to understand the safety of and/or how well the medicine works (efficacy).

Previously, the terms clinical study and clinical trial were used synonymously. Refer to Regulation 2014/536 for more information.

Clinical study report

A clinical study report is a document containing extensive detail about the plan, methods and conduct of the study so that it is clear how the study was carried out. This report should provide a clear explanation of how the design features of the study were chosen and include results of the trial. A clinical study report should also provide enough individual patient data, to allow the key analyses of data to be repeated, should the regulatory authorities wish to do so. It is a central part of any application for a new medicine to receive marketing authorisation, and it must meet the requirements of the regulatory authority that has to assess the application.

Clinical trial

A clinical trial is a clinical study in which participants are assigned according to a pre-defined therapeutic strategy or plan (protocol) to receive a health-related intervention, such as a medicine, in order to investigate its effects on health outcomes, usually compared to another (or sometimes no) treatment.

Clinical trials are used to evaluate clinical practices that do not fall within the current practices of a country, or to evaluate a new medicine (investigational medicinal product).

Clinical trials are used to generate data on the safety and efficacy of the intervention.

Clinical trials are conducted only after a regulatory authority approval and ethics committee review. Clinical trials are often characterised in Phases from I (first-in-human), II (exploratory), III (confirmatory) to IV (post approval).

Previously, the terms clinical study and clinical trial were used synonymously. Refer to Regulation 2014/536 for more information.

Clinical trial authorisation

Before a clinical trial can start, the sponsor must apply for and be given clinical trial authorisation (CTA). Each European country has its own regulatory authority that assesses applications for clinical trial authorisations. For clinical trials that will take place in more than one European country, there is a Voluntary Harmonisation Procedure which allows one application to be submitted to the authorities in all the relevant countries.

As well as clinical trial authorisation, a positive opinion from an ethics committee (or institutional review board) is needed before a clinical trial can go ahead.

Clinician-reported outcome

A type of outcome assessment determined by a trained health-care professional after observation of a patients health condition.

Cohort studies

Cohort studies are used to study how common diseases are, their causes, and their prognoses. Cohorts are groups of people who are selected on the basis of certain characteristics. For example, if exposure to a risk factor such as cigarette smoke is suspected to cause a disease, a cohort can be selected in which one group has been exposed and another group has not. Both groups are then studied for signs or symptoms of disease.

Cohort studies can be prospective (cohorts are identified before any signs of disease and are followed up over time) or retrospective (data is used that has already been collected, possibly over a long period of time).

Cohort studies are a kind of observational study, in which the researcher does not perform any intervention (such as administering a medicine).

Cohort studies are useful when it would be unethical to carry out a randomised controlled trial (RCT). For example, deliberately exposing people to cigarette smoke or asbestos would be unethical and therefore cannot be done.

Common technical document

The Common Technical Document (CTD) is an internationally agreed format for the preparation of marketing applications to regulatory authorities for new medicines approval. The CTD is divided into five modules, where modules 2 to 5 constitute the actual CTD; and module 1 differs according to the region. The modules are:

- Administrative and prescribing information (these contents might differ based on national requirements),
- Overview and summary of modules 3 to 5,
- Quality (pharmaceutical documentation),
- Non-clinical study reports (pharmacology/toxicology),
- Clinical study reports efficacy and safety (clinical trials).

Compassionate use

Method of providing an unlicensed medicine prior to final approval by a regulatory (competent) authority for use in humans. This procedure is used with very sick individuals who have no other treatment options. Often, case-by-case approval must be obtained for compassionate use of a medicine or therapy.

Concomitant

Something that exists or occurs at the same time as something else. It can be a natural event, but in medicine is used when referring to:

- Concomitant medication: two or more medicines are given at the same time when treating diseases, or
- Concomitant disease: a second disease (or more) is present at the same time as the primary disease (or secondary symptoms occur with a main symptom).

Confidence Interval

A confidence interval is an estimated range of values in which all data (results) are likely to lie. For a given treatment effect measured in a trial on a sample of a population, the confidence interval can be calculated to give a best estimate range of the treatment effect that will be seen in the whole population.

The likelihood that the confidence interval will contain the value is called the confidence level. Traditionally, confidence levels are set at 95% or 99%. This means that researchers are 95% (or 99%) certain that the measured effect lies within the true range.

For example, instead of estimating the mean age of a population as 15 years, researchers say that the mean age is between 14 and 16. This confidence interval contains the true value being estimated.

Confirmatory studies

These are studies conducted in Phase III of the clinical development of a medicine. They aim to confirm the efficacy and safety in a large patient population. They can involve thousands of patients, can be run in many countries, require a huge amount of expertise to be run effectively, and are therefore resource-intense and very time consuming. They are the largest, most complicated, and most expensive part of the development of a medicine.

Continuous endpoint

A measurement, often expressed in numbers, collected in a clinical trial that represents a specific variable. Unlike binary endpoints which are expressed by "yes" or "no" (e.g. survived against dead), continuous endpoints are expressed by measurement on a continuum of possible values over time (e.g. blood pressure or months of survival).

Contract research organisation

A contract research organisation (CRO) is an independent organisation that provides support into the medicines development process. Typically, a CRO will organise and conduct clinical trials to test an investigational medicinal product in humans.

Cost effectiveness

In the context of pharmacoeconomics, cost effectiveness is studied by looking at the results of different interventions by measuring a single outcome, usually in natural units (for example, life-years gained, deaths avoided, heart attacks avoided, or cases detected).

Alternative interventions are then compared in terms of cost per (natural) unit of effectiveness in order to assess how it provides value for money. This economic evaluation helps decision-makers to determine where to allocate limited healthcare resources.

Cost effectiveness, however, is only one of a number of criteria that should be used to determine whether or not interventions are made available. Other issues, such as equity, needs, and priorities should also be part of the decision-making process.

Data exclusivity

Data exclusivity refers to the period during which the data of the original marketing authorisation holder is protected. It is the time during which another company cannot use the originators data in support of another marketing authorisation application, i.e.: generics, hybrids, biosimilars. Therefore, competent authorities may not accept such an application during this period of time. In Europe, this protection period lasts for a minimum of eight years and is intended to incentivise innovation.

Decentralised procedure

The decentralised procedure is a process for authorising medicines in more than one European Union member state at the same time.

Development safety update report

The Development Safety Update Report is an annual review of safety information during clinical trials of a medicine under investigation whether or not it is marketed. The main objectives of a Development Safety Update Report are to:

- Summarise the current understanding and management of identified and potential risks.
- Describe new safety issues that could have an impact on the protection of clinical trial participants.
- Examine whether any new safety information is in line with previous knowledge of the product's safety.
- Provide an update on the status of the clinical investigation/development programme and study results.

Disability-adjusted life year

The disability-adjusted life year (DALY) is a measure used in health economics. It represents the burden of a disease, expressed as the number of years lost due to ill-health, disability, or early death. One DALY can be thought of as one lost year of healthy life.

The total of DALYs across a population can also be thought of as a measurement of the gap between the population's current health status and an ideal situation in which every person enjoys perfect health into old age.

Disease burden

Also known as unmet need or therapeutic need?. It may be a measure of the number of people affected by a particular disease for whom current treatments are inadequate. It may include the number of new diagnoses of a disease, or the costs to society or a government representing those affected. It may also include more qualitative aspects about the burden of disease and current treatments available to patients.

Dosage forms

Dosage forms of a medicine are the means (or the form) by which drug molecules are delivered to sites of action within the body. There are several types of dosage form, depending on the method/route of delivery of the medicine. These include for instance pills, capsules, syrups, suppositories and solutions for injection. Typically this involves a mixture of the active substance(s) and non-active substances (excipients).

Dosage regimen

The dosage regimen is the schedule of doses of a medicine, including the time between doses, the duration of treatment and the amount to be taken each time. Dosage regimens also include how a medicine is to be taken, and in what formulation (dosage form).

Dose

A dose is a single, measured amount of a medicine to be taken at one time. This can be expressed as the forms (e.g. 1 capsule, 1 suppository), weight (e.g. 250 mg), volume (e.g. 10 mL, 2 drops), or some other quantity (e.g. 2 puffs).

Double blind

Double blinding is a method used in clinical trials to reduce the risk of bias, which can be caused intentionally or unintentionally when trial participants and/or researchers are aware of which participants are receiving which treatment (or placebo).

For example, in a trial with one treatment group and one placebo group, blinding means that the participants do not know which group they have been assigned to. In a double blind trial, neither the research team nor the participants know which participant is assigned to which group.

Sometimes the term single blind is used to describe studies in which the participants are unaware of which group they are in but the research team is aware.

Drug candidate

In medicines development, the drug candidate is the molecule among several that has been shown to have sufficient target selectivity and potency, and favourable medicine-like properties and justifies further development. It will then be subjected to a new series of tests, and non-clinical studies and clinical trials. At this stage it is not yet a medicine.

Drug development

Drug development is the process of bringing a new medicine to the market once a drug candidate (lead compound) has been identified in drug discovery. It includes non-clinical tests on microorganisms and animals, application to the regulatory authority to initiate clinical trials on humans, and may include the step of obtaining regulatory approval with a Marketing Authorisation Application to market the drug. It is also known as medicines development. EUPATI uses the term medicines development throughout its texts.

Drug distribution

The process by which a medicine is distributed from one location to another within the body. See also pharmacokinetics.

Drug substance

An ingredient intended to exert pharmacologic action or other direct effect in the diagnosis, cure, mitigation, or prevention of disease or to affect any function of the body. Along with other ingredients (excipients) it is used to formulate a medicinal product.

Drug tolerance

Tolerance of a medicine may be considered as the ability of the body to endure a certain dose of a medicine. In contrast, drug tolerance refers to a decreasing response to repeated constant doses of a medicine, or the need for increasing doses to maintain a constant response. Drug tolerance can lead to physical (physiological) or emotional dependence, which is an adaptive state associated with a withdrawal syndrome on cessation of repeated exposure to a medicine.

Effectiveness

The capability of a medicine to produce a desired or expected effect in the real world clinical setting. When talking in terms of efficacy vs. effectiveness, effectiveness relates to how well a treatment works in the practice of medicine, as opposed to efficacy, which measures how well a treatment works in clinical trials or laboratory studies.

Efficacy

Efficacy refers to the ability of a medicine to provide a beneficial effect (a positive benefit/risk ratio) when studied in a clinical trial. When talking in terms of efficacy vs. effectiveness, effectiveness relates to how well a treatment works in the real world practice of medicine, as opposed to efficacy, which measures how well a treatment works in clinical trials or laboratory studies.

Efficiency

In the context of health economics, efficiency of a medicine is a measure of its ability to provide a beneficial effect against its costs to individuals or society. The most efficacious treatment may not be the most efficient (cost-effective) option, for example making it unaffordable for the patients or the health system to implement.

Eligibility

Eligibility in medicines development usually refers to the requirements that participants must meet in order for them to have the possibility of being selected to participate in a clinical trial. The requirements (criteria) will typically contain not only elements which allow participation (inclusion criteria) but also details of what will prevent someone from participating (exclusion criteria).

Endpoint

The endpoint of a clinical trial is a pre-defined event: for instance, the occurrence of a disease, the occurrence of a symptom, or a particular laboratory result. Once someone reaches the endpoint, they are generally excluded from further research in the trial.

Endpoints can be hard (objective) or soft (subjective). In some cases they can be replaced by surrogate endpoints. The endpoints used in a trial must be defined and documented as part of the trial protocol.

Epigenetics

Epigenetics is the study of changes in gene activity (expression) that do not involve changes in the underlying DNA sequence (genotype). Epigenetic changes are a regular and natural occurrence, but they can also be influenced by several factors including age, environment/lifestyle, and disease state through mechanisms that switch genes on or off.

Epigenomics

Epigenomics is the study of the complete set of epigenetic modifications on the genetic material of a cell, known as the epigenome. The epigenome marks the genome in two main ways, both of which play a role in turning genes on or off.

In epigenomics, researchers try to chart the locations and understand the functions of all the chemical tags that mark the genome. Epigenomic maps may someday help doctors make diagnoses and tailor a patients response to therapies.

Ethics committee

An ethics committee is an independent body made up of a range of individuals including medical or scientific professionals and non-medical or non-scientific members (e.g. patients or lay members). An Ethics Committee may operate within an institution, or it may be national, or supranational or private.

Ethics committees have a responsibility to ensure the protection of the rights, safety and wellbeing of research participants, as well as assuring the public of that protection. It operates, among other things, expressing an opinion on the clinical trial protocol, the suitability of the investigators involved in the trial, the adequacy of facilities, and on the methods and documents to be used to inform trial participants and obtain their informed consent. A trial should only begin when a favourable opinion by an Ethics Committee has been given.

Ethics Committees may also monitor studies once they have begun and once they are complete.

EU regulation

A regulation is a written rule or law. European regulations are binding legislative acts. They must be applied in their entirety across the EU simultaneously from the date agreed. Regulations can be distinguished from European directives which are legislative acts that set out a goal that all EU countries must achieve. However, it is up to the individual countries to devise their own laws on how to reach these goals. Directives need to be converted into national law before they are enforceable.

EUnetHTA

The European network for Health Technology Assessment was established to create a network for HTA across Europe, developing a framework (HTA Core Model) by which a technology (for example a new medicine) can be assessed. It facilitates efficient use of resources, creating a sustainable system of knowledge, and promoting good practice in HTA methods and processes. The network connects public national HTA bodies, research institutions and health ministries, to exchange information and to support policy decisions by member states.

European Public Assessment Report (EPAR)

A European Public Assessment Report (EPAR) is an assessment produced for all medicines where marketing authorisation is sought through the centralised procedure at the European Medicines Agency (EMA). It is a series of documents, and includes:

- a lay summary
- details about the marketing authorisation holder
- product information (such as the package leaflet and summary of product characteristics)
- details about the assessment carried out at EMA

EPARs are published on the EMAs website once the European Commission has issued a decision regarding a marketing authorisation.

Evidence-based medicine

Evidence-based medicine (EBM) applies the scientific method to medical practice, using techniques from science, engineering, and statistics - such as the meta-analysis of scientific literature, benefit-risk analysis, and randomised controlled trials. One of the goals of evidence-based medicine is that healthcare professionals should make conscientious, explicit, and judicious use of current best evidence in their everyday practice.

Exclusion Criteria

Exclusion criteria are characteristics that exclude people from taking part in a trial.

For example, depending on the requirements of the trial, exclusion criteria might include age, gender, type or stage of disease, and the presence or absence of other medical conditions. For a trial studying an anti-venom (snake bite) medicine, some of the criteria that would exclude an individual from taking part might be:

- Pregnancy
- Aged under 12 or over 70
- Previously received an anti-venom medicine
- Medical history includes wheezing, high blood pressure, heart disease
- Known adverse reaction to adrenaline.

Exclusion criteria (and inclusion criteria) are an important part of a trial protocol. If they are properly defined, exclusion and inclusion criteria will increase the chances of a trial producing reliable results. They also protect participants from harm and help avoid exploitation of vulnerable people (such as those unable to provide informed consent).

The reason for choosing the exclusion criteria should be documented with the trial protocol. Exclusion of certain groups can affect how realistic it is to generalise the trial results to the relevant patient population (external validity). This should be considered by researchers when they are designing a trial, and unnecessary exclusions should be avoided.

Factor V

A coagulation factor needed for the normal clotting of blood. Also known as proaccelerin. False positive A result that indicates that a given condition is present when it is not. An example of a false positive would be if a particular test designed to detect cancer returns a positive result but the person does not have cancer.

Formulation

A formulation is a mixture of different chemical substances prepared according to a specific method to create a medicinal product.

Formulation

A formulation is a mixture of different chemical substances prepared according to a specific method to create a medicinal product.

Fraud

Fraud is an intentional act of deception. An example of fraud within a research setting might be a deliberate attempt to fabricate data or present data in a misleading way. Fraud does not include honest errors or poor research processes, unless it is done with an intention to deceive. In research, fraud can impact the sponsor financially, have severe consequences for a study's credibility, and could even lead to patients accessing ineffective or harmful treatments.

Freeze-drying

Freeze-drying, also known as lyophilisation, is used to preserve a perishable material or make the material in a medicine more convenient for transport. It works by freezing the material and then allowing the frozen water in the material to change directly from the solid to the gas phase without passing through the intermediate liquid phase.

Futility

Futility is the inability of a clinical trial to achieve its objectives. Problems such as difficulty recruiting enough patients can mean that a trial will not give a result that can be properly statistically analysed. If such problems are discovered during the trial, it may be appropriate to stop the trial early. This kind of calculation is known as a futility assessment, and is one kind of interim analysis. Stopping a trial early because it is unlikely to achieve a statistically reliable result is ethically appropriate because it prevents exposure of patients unnecessarily to treatments or other interventions. It can also save time and therefore costs.

GDPR

Refer to Regulation (EU) 2016/679 for more information.>EU General Data Protection Regulation (GDPR) replaces the Data Protection Directive 95/46/EC and was designed to harmonise data privacy laws across Europe, to protect and empower all EU citizens data privacy, and to reshape the way organisations across the region approach data privacy. The final Regulation provides more rights to citizens to be better informed about the use made of their personal data, and gives clearer responsibilities to people and entities using personal data.

GDPR covers patients fundamental right to protection of their health data and is an important issue in diverse contexts such as healthcare, including care given through eHealth or in a cross-border healthcare context, and research (clinical trials, clinical investigations, epidemiological research, patient registries, etc). Health and genetic data belong to the category of sensitive data, and benefit from additional protection.

Refer to Regulation (EU) 2016/679 for more information.

Gene therapy

Gene therapy is an experimental technique that replaces a faulty gene in a cell, or adds a new gene to cure or prevent disease. In the future, this technique may allow doctors to treat a disorder instead of using medicines or surgery. Researchers are testing several approaches to gene therapy, including replacing a mutated gene that causes disease, deactivating a mutated gene that is not properly functioning, or introducing a new gene into the body to help fight a disease.

Although gene therapy is a promising treatment option for a number of diseases, the technique is still under study to make sure that it will be safe and effective. Gene therapy is currently only being tested for the treatment of diseases that have no other cures.

Generic medicine

A generic medicine is a medicine that is developed to be the same as a medicine that has already been authorised, called the ‘reference medicine’.

A generic medicine contains the same active substances as the reference medicine, and it is used at the same doses to treat the same diseases. However, a generic medicine’s inactive ingredients, name, appearance, and packaging can be different from the reference medicine’s.

Generic medicines are manufactured according to the same quality standards as all other medicines.

A company can only develop a generic medicine for marketing once the period of exclusivity on the reference medicine has expired. This is usually 10 years from the date of first authorisation.

Each medicine has an approved name called the generic name. A group of medicines that have similar actions often have similar-sounding generic names. For example, phenoxymethylpenicillin, ampicillin, amoxicillin, and flucloxacillin are in the same group of antibiotics.

Gold standard

In medicines development, the gold standard often refers to the best available therapy/product/treatment. Depending on the context, the gold standard may also mean different things. In clinical design, a double-blind, randomised trial is seen by many as the gold standard.

The gold standard may change over time as new methods/treatments/medicines become available. For example, the gold standard test for the diagnosis of aortic dissection (a tear inside the aorta) used to be the aortogram, which had a sensitivity as low as 83% and a specificity as low as 87%. Now, the magnetic resonance angiogram (MRA) is seen by many as the new gold standard test for aortic dissection, with a sensitivity and a specificity both over 90%.

Good clinical practice

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve human participants. The International Conference on Harmonisation (ICH) has issued a guideline with the objective to provide a unified standard to facilitate the mutual acceptance of clinical data by the regulatory authorities in the jurisdictions pertaining to the ICH.

Group sequential design

Group sequential design is an example of a statistical approach in clinical trial design. It means that the sample size of the trial is not fixed in advance, and data is sequentially evaluated as it is collected. This is known as interim analysis, and might be carried out at several points in time. The trial can be stopped when significant results are seen, or if the interim analysis shows that there are safety concerns, or that the trial will not in fact be able to give a significant result. In this case no more recruitment of patients or further sampling from the patients involved will occur.

Before the trial starts, the stopping rule (i.e. the reason for stopping) must be documented and explained. The stopping rule is a description of exactly what the interim analysis must show to cause the trial to be stopped.

Group sequential analysis can lead to a conclusion much earlier than would be possible with a classical design. It can therefore save time and resources, and reduces the exposure of patients to inferior treatments.

Guarantee-time bias

Guarantee-time bias

Half-Life

The time required for half the amount of a medicine to be eliminated from the body.

Hard Endpoint

The endpoint of a clinical trial is a pre-defined event: for instance, the occurrence of a disease, the occurrence of a symptom, or a particular laboratory result. Once someone reaches the endpoint, they are generally excluded from further research in the trial. A hard endpoint is an endpoint that is well defined and can be measured objectively. For example, in cancer research, the endpoint in a trial might be related to response to treatment (such as shrinkage of a tumour). Endpoints related to a response are typical in Phase II clinical trials for cancer treatments. Endpoints relating to the survival of patients are common in Phase III cancer trials. Progress free survival and disease free survival measure the length of time patients are alive without their disease worsening. In contrast to hard endpoints, soft endpoints are subjective measures.

Hazard ratio

A hazard ratio is a measure of how often a particular event happens in a defined period of time in one group compared to how often it happens in another group.

Hazard ratio

A hazard ratio is a measure of how often a particular event happens in a defined period of time in one group compared to how often it happens in another group.

Health event

A health event can be positive or negative. An example of a health event is the development of a disease, an injury, or responding to a medicine

Health event

A health event can be positive or negative. An example of a health event is the development of a disease, an injury, or responding to a medicine.

Health Technology Assessment (HTA)

Health technology assessment aims to inform decision making by health care policy makers. It is a systematic process that considers health technologies (such as medicines) and can involve a review of:

- clinical evidence compared to existing models of care,
- cost effectiveness,
- social and ethical impacts on the health care system and the lives of patients.

The process advises whether or not a health technology should be used, and if so, how it is best used and which patients are most likely to benefit from it. Assessments vary, but most look at the health benefits and risks of using the technology. They can also look at costs and any other wider impacts that the technology may have on a population or on a society. They can also look at the relationship between costs and benefits and risks, and make determinations about value for money.

Health-Related Quality of Life

Health-Related Quality of Life considers many different aspects related to a person’s perception of quality of life affected by health status. These include physical, psychological, functional, and social aspects.

Health-Related Quality of Life

Health-Related Quality of Life considers many different aspects related to a persons perception of quality of life affected by health status. These include physical, psychological, functional, and social aspects.

Herd immunity

Herd immunity is a form of immunity that occurs when the vaccination of a significant portion of a population (or herd) provides a measure of protection for individuals who have not or cannot develop immunity.

Hypothesis

A hypothesis is an assumption, or set of assumptions, made on the basis of limited evidence that either:

a) asserts something as a starting point for further investigation; or

b) confirms something as highly probable in light of established facts.

For a hypothesis to be a scientific hypothesis, it is required that one can test it. A working hypothesis is a provisionally accepted hypothesis proposed for further research.

For the purposes of medicines development, the interest is in the hypothesis that asserts something for example that a new treatment for a disease is better than the existing standard of care treatment.

Identified risk

An adverse event for which there is adequate evidence of an association with the use of the medicinal product of interest.

Immunotoxicity

Immunotoxicity is harm occurring to the immune system caused by exposure to chemical substances. Testing for immunotoxicity is a standard part of developing substances as potential new medicines. Symptoms of immunotoxicity can include increased rates or severity of infectious diseases or cancer. Toxic agents can also cause autoimmune diseases, in which healthy tissue is attacked by the bodys own immune system. Allergy is another form of immunotoxicity, and many chemicals are known to induce allergic reactions in some people.

Incidence

The number of new cases of a health event (such as development of a disease, or reaction to a medicine) that occur during a specific time period, usually a year, in a specified population. Incidence is therefore also a measure of the risk of experiencing the health event during a certain period of time.

Inclusion criteria

Inclusion criteria are the characteristics that potential participants must have in order to be considered for participation in a trial. They describe the patient population and patient selection criteria.

Inclusion criteria should specify the type of testing used to make the patients diagnosis, as well as specific disease requirements (for example, how severe the disease is, failure or success with previous treatments, plus any other factors that might affect prognosis such as age, sex, or ethnicity).

The inclusion criteria (and exclusion criteria) are important parts of a trial protocol. If they are properly defined, inclusion and exclusion criteria will increase the chances that the trial produces reliable results. They also protect participants from harm and minimise the risks.

Indication

In medicine, indication refers to a health condition (therapeutic area) for which a specific intervention (medicinal product, medical device, treatment, procedure) is developed to cure, relieve symptoms, prevent or diagnose. The indication, as specified in the Summary of Product Characteristics (SmPC) document, determines the boundaries of lawful use of such medicinal product.

Intermediate endpoint

In clinical trials, intermediate endpoints are measures that may be associated with disease status or progression toward a primary endpoint (such as mortality or morbidity). It may be a measure of a body function or disease symptoms (e.g. measures of lung function in chronic obstructive pulmonary disease (COPD)) that is expected to correlate with changes observed on primary endpoints. Clinical trials are often designed to measure changes of an intermediate endpoint and evaluate the effects of an intervention on clinical outcomes.

International Council for Harmonisation

Formerly the International Conference on Harmonisation. The International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) produces harmonised guidelines for global pharmaceutical development, and their regulation. It brings together the regulatory authorities and the pharmaceutical industry from five regions (Europe, Japan, USA, Canada and Switzerland).

ICH has been established in order to reduce the duplication of clinical trials and create a more streamlined regulatory assessment process for new applications. As such, ICH has developed four sets of guidelines provided for specific topics including quality, safety, efficacy and multidisciplinary (e.g. ICH medical terminology (MedDRA), or the Common Technical Document (CTD)) which are implemented by the regulatory authorities of its membership.

Intervention

In medicine, intervention is an action which changes the outcome or course of a condition or disease so as to prevent harm or improve health through the use of treatments, medicinal products, medical devices or procedures/surgery.

Interventional study

An interventional study is one in which the participants receive some kind of intervention, such as a new medicine, in order to evaluate it. In the medicines development process, medicines are evaluated through interventional studies known as clinical trials.

There are many variations in how clinical trials are designed, but they are commonly randomised (participants are allocated to different arms in the study randomly) and controlled (the study medicine is given to one arm, and the outcomes are compared with an alternative treatment or placebo given to another arm). These are called randomised controlled trials, or RCTs.

Intravenous

Intravenous means within the vei. It is the infusion of liquid directly into a vein using a syringe or intravenous catheter (tube).

Compared with other routes of administration, the intravenous route is the fastest way to deliver fluids and medicines into the blood stream (the systemic circulation). In intravenous therapy, the bioavailability of the medication is 100%.

Investigational medicinal product

An investigational medicinal product is an active ingredient or placebo that has been pharmaceutically formulated (prepared) for human use which is being tested, or used as a comparator, in a clinical trial.

Typically IMPs have not yet received marketing authorisation, however in some circumstances they may be products that have been authorised:

- when they have been made using a different formulation than that which is authorised (e.g. different dose)
- when the authorised product is to be used as the test substance or comparator in a clinical trial
- when used for an unapproved indication (off-label), or
- when used to gain further information about an approved use

Investigational medicinal product dossier

The Investigational Medicinal Product Dossier (IMPD) is an evolving document containing currently available information about an investigational medicinal product (IMP). It includes summaries of information related to the quality, manufacture and control of any IMP (including reference product and/or placebo), data from non-clinical studies and from its clinical use, and the products phase of development.

Investigational plan

An investigational plan is a medicines development plan to support the authorisation of a medicine for humans. It aims to ensure that the necessary data is obtained through clinical and other studies.

Life years gained

Life years (LY) gained is a measure in health economics. It expresses the additional number of years of life that a person lives as a result of receiving a treatment.

Lifetime prevalence

Lifetime prevalence is the proportion of a population that, at some point in their life, has experienced a particular health event, risk factor or disease. For example, in a survey, you might be asked if you have **ever** smoked. Lifetime prevalence is calculated by comparing the number of people found to have experienced the health event with the total number of people studied.

Malignant

A tumour is malignant if it is able to invade tissue other than where it originally grew (the primary site). Malignant tumours may spread (metastasise) to nearby tissues, or via the blood stream to other parts of the body quite distant from the primary site. New tumours can then form at those new sites. Benign tumours are not cancerous: their cells do not spread to other parts of the body.

Market exclusivity

The 10-year period after the marketing authorisation of an **orphan medicine**, during which similar medicines for the same indication cannot be placed on the market. Market exclusivity should not be confused with market protection or data exclusivity, market exclusivity refers only to orphan medicines.

In this period, the EMA (the Agency) and the member states shall not accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product. This protects the original marketing authorisation holder from market competition with similar medicines with similar indications once they are approved and is intended to encourage the development of medicines for rare diseases.

The period of market exclusivity is extended by two years for medicines that also have complied with an agreed paediatric investigation plan (PIP).

Marketing authorisation

Marketing authorisation (MA) refers to the approval for a medicine to be marketed.

A system of marketing authorisation was put in place to protect public health. Marketing authorisations are granted only when a competent authority (or regulatory authority) has conducted a scientific evaluation, and is satisfied that a medicine is sufficiently safe and effective, and of high enough quality.

Different procedures exist to obtain a MA. The EMA (the Agency) is responsible for the centralised procedure. A single application is submitted to the EMA for evaluation by the Agencys Scientific committees. If the assessment is positive, a single marketing authorisation is issued by the European Commission. The Marketing Authorisation Holder can then legally begin to market the medicine in all EEA (European Economic Area) countries (EU *member states* and the three *EEA* EFTA States (Iceland, Liechtenstein, and Norway).

National Competent Authorities (NCAs) are responsible for evaluation of marketing authorisation applications and granting MAs for medicines that fall outside the scope of the centralised procedure. Companies can apply for authorisation of these medicines in several countries simultaneously, using the decentralised procedure, or, once a medicine is authorised in one EU member state, a company can apply for this authorisation to be recognised in other EU countries (the mutual recognition procedure). These procedures result in national MAs for each member state involved.

Marketing Authorisation Holder (MAH)

A Marketing Authorisation Holder (MAH) is a company, firm or non-profit organisation that has been granted a marketing authorisation. The marketing authorisation allows the holder to market a specific medicinal product, in one or more EU member states. Once a medicinal product is marketed and in use by patients, the MAH continues to be responsible for monitoring safety (pharmacovigilance). Any suspected adverse reactions must be reported to the body which granted the marketing authorisation, in the form of a periodic safety update report (PSUR).

Maximum tolerated dose

The maximum tolerated dose (MTD) is the highest dose of a medicine or treatment that will produce the desired effect without resulting in unacceptable side effects. It is determined in clinical trials by testing increasing doses on different groups of people until the highest dose with acceptable side effects is found. Establishing the maximum tolerated dose is the main objective of Phase I clinical trials.

Medical device

A medical device is an instrument, apparatus, implant, software or related article used to diagnose, prevent, or treat disease or other conditions. It must not achieve its primary intended action in or on the human body through pharmacological, immunological or metabolic means, but may be assisted in its function by such means.

Medical devices vary greatly in complexity and application. They are intended by the manufacturer to be used for:

- Diagnosis, prevention, monitoring, treatment, or alleviation of disease.
- Diagnosis, monitoring, treatment, alleviation of, or compensation for an injury or handicap.
- Investigation, replacement, or modification of the anatomy or of a physiological process.
- Birth control.

Medical subject headings

Medical Subject Headings (MeSH) is an online controlled vocabulary that lists words, groups of synonyms and related concepts, for the purpose of indexing journal articles and books in the life sciences that facilitates searching.

It was created and updated by the United States National Library of Medicine (NLM), it permits searching at various levels of specificity and allows retrieval of documents in different languages. MeSH is also used by ClinicalTrials.gov registry to classify which diseases are studied by trials registered in ClinicalTrials.gov.

Medical technology assessment

The objective evaluation of a medical technology regarding its safety and performance, its (future) impact on clinical and non-clinical patient outcomes as well as its interactive effects on economical, organizational, social, juridical and ethical aspects of healthcare. Medical technologies are assessed both in absolute terms and in comparison to other (combinations of) medical technologies, procedures, treatments or doing-nothing.

Medicines development

The term medicines development refers to the scientific and regulatory processes put in place in the attempt to bring a new medicine to the market. It is often used synonymously with drug development. EUPATI has chosen to use the term medicines development throughout its texts.

Medicines regulation

Medicines regulation is a system that promotes and protects public health. It applies scientific knowledge and is based on national and international laws, to prevent the use of medicines that do not work, are of poor quality, and/or that may be harmful.

Systems vary around the world but generally medicines regulation aims to:

- Assess the safety, efficacy and quality of medicines, and issue marketing authorisations.
- License and monitor manufacturers and dispensers of medicines.
- Monitor the quality of medicines.
- Monitor the safety of medicines under development and in general use including collecting and analysing adverse reaction reports.
- Provide independent information on medicines to professionals and the public.

Metastasis

Metastasis is the spread of tumour cells from the original site (the primary site) to another part of the body. Tumours can metastasise by invading nearby tissue, or by spreading through the circulation (blood and lymphatic system).

Multi-Arm Multi-Stage (MAMS)

Multi-Arm Multi-Stage (MAMS) trials have a specific design that allows for several different treatments to be evaluated simultaneously against the standard treatment in a single trial.

Mutual recognition procedure

The mutual recognition procedure is the system for medicines authorisation by individual member states (Concerned Member States) recognising the authorisation of another member state (the Reference Member State) which has evaluated and authorised a new medicine.

National competent authority

A National competent authority or regulatory authority has the power to grant marketing authorisations for medicinal products in its territory.

National competent authorities are organisations that have the legally delegated or invested authority, or power to perform a designated function, normally monitoring compliance with the national statutes and regulations.

New drug application

A New Drug Application (NDA) is a document submitted to the Food and Drug Administration (FDA) to request authorisation to market a medical product in the United States. The information in the NDA must allow the FDA to make the following judgements (quoted from FDA website):

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks
- Whether the drugs proposed labelling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drugs quality are adequate to preserve the drugs identity, strength, quality, and purity.

The NDA must include information about the medicines ingredients, outcomes of the animal and clinical studies, how it behaves in the body, and how it is manufactured and packaged.

New Molecular Entity

New Molecular Entities (NMEs) are compounds that emerge from the process of medicine discovery, that are not a version or derivative of an existing, previously investigated/approved substance. They have promising activity against a particular target thought to be important in a disease, however, little is known about the efficacy, safety, toxicity, pharmacokinetics and metabolism in humans. A full development programme of non-clinical and clinical trials must be performed to evaluate the potential of an NCE to become a medicinal product.

No observed adverse effect level

The no observed adverse effect level (NOAEL) is the highest tested dose of a medicine at which there is no increase in the frequency of any adverse effects (biological or statistically significant) when compared to its control.

Although the NOAEL approach involves some consideration of pharmacokinetics and pharmacodynamics properties, its focus is on the estimation of the highest safe dose, looking for a safety window based on toxicological threshold.

Non-clinical testing

Non-clinical testing is conducted at a stage of medicines development that uses animals and/or cells or tissues. It does not involve testing in humans. The main goal of non-clinical tests is to determine the safety of a medicine. Non-clinical testing will investigate any harmful effects of the medicine on the body due to the medicines pharmacology, such as:

- Toxic effects - for example, on the reproductive system
- If the medicine causes genetic changes
- For some substances, whether they might cause cancerous growth.

Toxicity will be measured in relation to different doses, or length of use of the medicine. The reversibility of any toxicity will also be studied.

Information from non-clinical testing is used in planning clinical trials in humans. It is used to decide what the starting dose should be, and the range of does to be tested. It also suggests what clinical signs should be looked for in order to detect any adverse effects.

Non-interventional observational study

In epidemiology and statistics, an observational study draws conclusions about the possible effect of a treatment on participants, where the assignment of participants into a treatment group versus a control group is outside the control of the investigator. In a non-interventional observational study, no additional diagnostic or monitoring procedures are applied to the patients, and epidemiological methods are used for the analysis of collected data (as per Article 2(c) of 2001/20/EC). It is not a randomised, controlled trial (RCT).

However, in some cases, observational studies are the most appropriate design for example, if the condition being studied is rare. Sometimes non-interventional studies are the only ethical approach, for example if the effect of an environmental risk factor such as asbestos is being studied, it would be unethical to deliberately expose participants to asbestos.

There are three types of non-interventional study, which are defined separately in this glossary. They are:

- Cohort studies
- Cross-sectional studies
- Case-control studies

Non-randomised trial

In a non-randomised clinical trial, participants are allocated to different treatment (or placebo) arms using a non-random method. Allocation is decided and managed by the investigator. Non-random allocation can lead to bias in the results of a trial.

In the description above, the non-randomised trial is controlled (arms receiving an intervention are compared with arms that are receiving different interventions or placebo). There are several other trial designs that are non-random, but controlled. These include prospective observational studies.

Number-needed-to-treat

The number-needed-to-treat (NNT) is a measure used to describe the effectiveness of an intervention, such as treatment with a medicine.

The NNT is the number of participants who will need to be treated in order for one person to recover, or show symptom reduction, or whatever outcome is being measured in the trial. A perfect result would be that every patient has a good outcome, and this would give an NNT of 1 . A large NNT means that the treatment is only effective in a small number of people: An NNT of 100 means that of 100 people treated, only 1 will have a favourable outcome.

One advantage of NNTs is that they can be easily compared for different medicines or interventions.

Observational study

In epidemiology and statistics, an observational study draws conclusions about the possible effect of a treatment on participants, where the assignment of participants into a treatment group versus a control group is outside the control of the investigator.

However, in some cases observational studies are the most appropriate design for example if the condition being studied is rare. Additionally, non-interventional observational studies are sometimes the only ethical approach. For example, if the effect of an environmental risk factor (such as asbestos) is being studied, it is unethical to deliberately expose participants to that risk factor.

In a non-interventional observational study, no additional diagnostic or monitoring procedures are applied to the participants, and epidemiological methods are used for the analysis of collected data (as per Article 2(c) of 2001/20/EC). A non-interventional observational study is not a randomised, controlled trial (RCT).

Observer-reported outcome

A measurement based on an observation by someone other than the patient or a health professional such as a parent, or other non-clinical caregiver who regularly observes the patient in daily life and is in a position to report on a specific aspect of the patients health.

This type of measure or observer report is without medical judgment or interpretation, and includes events or behaviours that can be observed in patients who cannot communicate themselves (e.g. infants or cognitively impaired).

Off label use

Off-label use refers to situations where a medicinal product is intentionally used for a medical purpose other than what is stated in the authorised product information, i.e. the Summary of Product Characteristics (SmPC).

Examples of off-label use include non-authorised:

- indication
- age group
- dosage
- route of administration

Orodispersible tablet

A tablet designed to be dissolved in the mouth rather than swallowed whole.

Orphan designation

Orphan designation is a special status for a medicine used to treat a rare disease or condition. An orphan designation is adopted by the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) and confirmed by the European Commission (EC) before the granting of marketing authorisation.

To qualify for orphan designation, a medicine must meet a number of criteria:

(1) It must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating.

(2) The condition must affect no more than 5 in 10,000 people in the EU, or it must be unlikely that sales of the medicine will be sufficient to justify the investment needed for its development.

(3) No satisfactory method of diagnosis, prevention or treatment of the condition exists, or, if it does, the medicine in question must provide a significant benefit to those affected by the condition.

Developers of medicines who obtain orphan designation benefit from a number of incentives. Incentives include specific scientific advice and 10-year market exclusivity. Market exclusivity means that, during this period, no other medicine for the same condition will be granted market authorisation. Reduced fees for applications for services from the European Medicines Agency (EMA) may also be available.

Orphan medicine

An orphan medicine is a medicine that has been developed specifically to treat a rare condition (an orphan disease). Orphan medicines generally follow the same regulatory development path as any other medicine, however, some incentives are provided to encourage a manufacturer to invest in developing them. An orphan designation is adopted by the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) and confirmed by the European Commission (EC) before the granting of marketing authorisation.

To qualify for orphan designation, a medicine must meet a number of criteria:

(1) It must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating.

(2) The condition must affect no more than 5 in 10,000 people in the EU, OR it must be unlikely that sales of the medicine will be sufficient to justify the investment needed for its development.

(3) No satisfactory method of diagnosis, prevention or treatment of the condition exists, or, if it does, the medicine in question must provide a significant benefit to those affected by the condition.

The incentives for developing orphan medicines include specific scientific advice, and 10 year market exclusivity. Market exclusivity means that no other medicine for the same condition will be granted market authorisation during this period. Reduced fees for applications for services from the EMA may also be available.

Over expression

Over expression is when a gene is too active and produces too much of the protein it encodes. Normally a variety of molecular mechanisms ensures that genes are expressed at the appropriate levels at the right times. Many cancers arise through the over expression of key regulatory genes.

P-value

A p-value, which stands for probability value, is a statistical measure between 0 and 1. It is used for hypothesis testing. In clinical trials it is used to give an indication of whether a result observed may be due to chance, or not.

A significance level should be set before data collection begins, and is usually set to 5% (or 0.05), although other levels may be used depending on the study.

A result is then said to be statistically significant (and allows us to reject the null hypothesis) if it has a p-value equal to or less than the significance level. This is generally written as p = 0.05.
In calculating the p-value, we first assume that there really is no true difference between the two tested treatments,e.g. new versus standard treatment (the null hypothesis). We then calculate the likelihood (probability) that the difference we have observed is just due to chance if our supposition is true (that is, if there is really no true difference). This is the p-value.

So, the p-value is the probability to observe effects as big as those seen in the study if there was really no difference between the treatments. If p is small, the findings are unlikely to have arisen by chance and we reject the idea that there is no difference between the two treatments (we reject the null hypothesis). If p is large, the observed difference is plausibly a chance finding and we do not reject the idea that there is no difference between the treatments.

Package Insert

The Package Insert (formerly prescribing information) in the United States (USPI), is a document included inside the external packaging of a prescription or over-the-counter medicine to provide information for patients. In Europe, the patient information in the pack is the Package Leaflet (PL) (formerly called the Patient Information Leaflet (PIL)).

The document is subject to detailed regulatory specifications, including approved chemical and proprietary names, descriptions, and classifications; clinical pharmacology; approved indications and usages; contraindications; warnings; precautions; possible adverse reactions (side effects); drug abuse and dependence information; over-dosage discussion; dosage and administration instructions; formulations; and appropriate references.

Package leaflet

In the EU, medicinal products must be accompanied by outer and/or immediate packaging information (labelling) and a Package Leaflet (PL). The PL should be written in language understandable by the patient and must undergo readability testing. It contains:

- What medicine X is and what it is used for (identification of the medicinal product).
- What you need to know before you take/use X (contraindications and warnings and precautions for use: in children and adolescents; with other medicines; with food, drink, or alcohol; in case of pregnancy, breastfeeding, driving, and using machines; and any excipient warnings, if applicable.)
- How to take/use X (dosage and method/route(s) of administration; use in children and adolescents; frequency of administration; duration of treatment; information in case of overdose and/or missing a dose; and any withdrawal effects if applicable).
- Possible side effects of X
- How to store X (storage conditions; expiry date; warnings against using the product after the expiry date; and warnings against visible signs of deterioration, if applicable).
- Contents of the pack and other information (what X contains; what X looks like; contents of the package; pharmaceutical form; physical description; pack sizes; details of the Marketing Authorisation Holder (MAH) and manufacturer; a list of local representatives (all or none); the date on which the PL was approved; and a section on other sources of information - including product-related website for over-the-counter products if applicable).

Product information templates (latest update: June 2015 (version 9.1)) are published on the EMA website.

Pandemic

An outbreak of a disease affecting a large proportion of a population and occurring over a wide geographic area.

Parenteral

Medicines administered via any route other than the gastrointestinal tract (oesophagus, stomach, and small and large intestines). The most frequent are subcutaneous, intravenous and intramuscular injections, but medicines that are topically administered to the eye, ear, and skin or even inhaled may be broadly considered as parenteral.

Patient registry

A patient registry is a collection of information about individuals, usually those with a specific diagnosis or with specific risk factors for a disease. Some patient registries seek people with varying health levels who may be willing to take part in research about a particular disease. Registries can be funded and/or managed by government agencies, non-profit organisations, clinics, or commercial organisations.

Patient registries have multiple uses. For example, registries for rare diseases can be used to establish the basic characteristics of the disease, how it is managed in clinics, and what outcomes people experience. Other uses include helping to measure clinical effectiveness of treatments in real world settings, and investigating quality of patient care.

Clinical trial registries collect basic health information from people who agree to be contacted about taking part in future clinical trials. Volunteering for a registry does not mean a person has signed up for a clinical trial. Volunteering for a disease registry can sometimes become a first step toward taking part in a clinical trial, but registries and specific trials are not directly linked.

Patient selection

Patient selection can refer to how patients are matched with proposed treatments (in the clinic), or how patients are selected to take part in clinical trials.

For clinical trials, detailed inclusion and exclusion criteria are documented before recruitment of patients can begin. The inclusion and exclusion criteria are an important part of a trial protocol. If they are properly defined, inclusion and exclusion criteria will increase the chances of a trial producing reliable results. They also protect participants from harm and help avoid exploitation of vulnerable people (such as those without the ability to provide informed consent).

Patient years

The patient year (or person year) statistic is used in many clinical studies and statistical assessments of risk.

Patient years are calculated as follows: If 15 patients participated in a study on heart attacks for 20 years, the study would have involved 300 patient years (15 x 20). This number can be divided by the number of patients who have been affected by a certain condition or event. For example, if six of the patients had heart attacks, that would be equal to one heart attack for every 50 patient years in the study (300 / 6 = 50).

Looking at data in this way can reveal trends and allows researchers to communicate levels of risk. Many studies on new medicines express their findings using patient years. For example, if one serious side effect is experienced for every 1,000 patient years of a study, this might be considered an acceptable level of risk.

Patient-reported outcome

A patient-reported outcome (PRO) is a measure of the experience or view of a participant in a clinical study. It is not a clinical measure, or an assessment made by anyone else involved in the study. PROs are commonly collected by asking patients to fill in questionnaires, or by interviewing patients. Questionnaires or interview guides used as part of clinical studies should undergo extensive testing to ensure they are reliable and valid.

PROs can be used to assess, for example, symptoms as experienced by the patient, disability, quality of life, and other health perceptions.

There are many published PRO questionnaires dealing with aspects of quality of life. some have been developed for specific conditions or treatments. Some are designed to be general, such as the EuroQoL or EQ-5D, which has been translated into many languages and used extensively in clinical trials.

PRO is often used interchangeably with the term patient-reported outcome measure (PROM).

Patient-Reported Outcome (PRO) measures

Patient Reported Outcomes (PROs) are data reported directly by a patient on his or her own health condition, without interpretation by a doctor or anyone else. They are based on a patients perception of a disease and its treatment. The findings or outcomes can be measured in absolute terms (e.g. severity of a symptom, sign, or state of a disease or condition) or as a change from a previous measure.

Patient-reported outcome measures (PROMs) are the tools used to measure and collect data on PROs. Generally, findings are measured by a well-defined and reliable patient-reported outcome (PRO) instrument. The use of a PRO instrument is advised when measuring an aspect of the disease or condition that is best known by the patient or is best measured from the patient perspective.

Per protocol analysis

An analysis that is restricted to the participants who fulfil the protocol in terms of the eligibility, interventions, and outcome assessment. This analysis restricts the comparison of the treatments outcomes to the participants who adhered perfectly to the clinical trial instructions as stipulated in the protocol, i.e. completed the full treatment. If done alone, this analysis leads to bias because it does not consider participants who did not follow the protocol completely for any reason.

Performance-linked access system

A performance-linked access system is a system used to minimise known safety risks of a medicine, once it is on the market. These systems guide prescribing, dispensing, and use of the medicine.

They are put in place when products have significant or unique benefits in a particular patient group or condition, but when unusual risks also exist, such as irreversible disability or death. These systems can include:

- prescription only by specially certified healthcare practitioners,
- product dispensing limited to pharmacies or practitioners that are specially certified,
- product dispensing only after patients have, for example, undergone certain laboratory tests.

Period of exclusivity

A period of exclusivity refers to a time after a medicine is authorised during which no other similar medicines with the same indications (intended uses) may be authorised. This protects the medicine from competition during the period of exclusivity. There can be several separate market exclusivities relating to designated conditions.

The period of market exclusivity is extended by two years for medicines that have also complied with an agreed paediatric investigation plan (PIP).

Periodic benefit risk evaluation report

A periodic benefit risk evaluation report is a format of safety report described by the ICH-E2C(R2) guideline which is used as a basis for the EU Periodic Safety Update Report (PSUR). The report is produced by the marketing authorisation holder (the individual or business that is granted authorisation to market a medicine) at defined time points after a medicine has been given marketing authorisation.

The purpose of the report is to provide comprehensive and up-to-date information about the safety of a medicine. The report should summarise any new evidence on safety, efficacy and effectiveness that might affect the balance of risks and benefits. The PSUR communicates risk to regulatory authorities and identifies where risk management initiatives may be required.

Periodic Safety Update Report (PSUR)

A Periodic Safety Update Report (PSUR) is EU terminology for a Periodic Benefit Risk Evaluation Report (PBRER). It is produced by the marketing authorisation holder (the individual or business that is granted authorisation to market a medicine) at defined time points after a medicine has been given marketing authorisation.

The purpose of the report is to provide comprehensive and up to date information about the safety of a medicine. The report should summarise any new evidence on safety, efficacy and effectiveness that might affect the balance of risks and benefits. The PSUR communicates about risk to regulatory authorities and identifies where risk management initiatives may be required.

Personalised medicine

Personalised medicine (PM) is a medical model that proposes to customise medical decisions, practices, and treatments for the individual patient. It uses targeted medicines aimed at specific molecules that are involved in the patients disease and takes genetic, clinical, environmental, and lifestyle information about the patient into account. The aim is to select the best therapies for the individual patient to ensure the best outcome and reduce the risk of side effects.

Progress in understanding the link between genomics (and other molecular factors) and disease is an important part of the development of personalised medicine. Pharmaceutical companies are already producing some targeted medicines as a result.

Pharmacovigilance

Pharmacovigilance is the practice of detecting, assessing, understanding and preventing the adverse effects of medicines. Pharmacovigilance enhances patient safety and public health by providing reliable information on the risks and benefits of medicines.

Phase 0 trials

Phase 0 trials are conducted with sub-therapeutic doses to see if a medicine behaves in the body in the way that earlier laboratory studies (non-clinical trials) predicted.

Phase I trials

Normally, the first studies in humans with a new medicine are Phase I trials.

Phase I trials are usually conducted in a small number of healthy volunteers (although some trials recruit patients). The aim of Phase I trials is to find out the safe dose range, and to look for any side effects. The initial dose given will be very small, and gradually increased if no or only mild side effects are observed. A new medicine has to meet certain pre-set requirements before it can continue to Phase II trials. Phase I, II, and III trials are commonly known together as clinical development.

Phase II trials

Phase II trials are generally the first studies with a new medicine in patients. They are usually conducted in a small number of patients who are monitored closely. These trials are often larger than Phase I trials.

Phase II studies are designed to find out if the medicine has a beneficial effect on the disease in question: They might compare the new medicine to an existing treatment or to a placebo. They also set out to determine the best dose range and how often the medicine should be given, and investigate the best way to manage any side effects.

A new medicine has to meet certain pre-set requirements before it can continue to Phase III trials. Phase I, II, and III trials are commonly known as clinical development.

Phase III trials

Phase III trials are generally large (comprising thousands of patients) and involve several study sites, sometimes in different countries. They compare the new medicine to existing treatments or a placebo, in order to show the safety and efficacy of the new medicine. Most Phase III trials are randomised.

Phase I, II, and III trials are commonly known as clinical development. Phase III studies are critical to applications for marketing authorisation.

Phase IV trials

Phase IV trials are usually conducted after marketing authorisation is granted and the medicine is in general use.

Phase IV studies are also known as post-authorisation safety studies (PASS) and may be voluntary or imposed by the regulatory authorities. The possibility also exists of requesting the marketing authorisation holder to conduct post-authorisation efficacy studies (PAESs) in order to complement efficacy data that are available at the time of the initial authorisation. Phase IV studies collect additional information about side-effects and safety, long-term risks and benefits, and/or how well the medicine works when used widely.

Physical health

Physical health is defined as the condition of your body, taking into consideration everything from the absence of disease to fitness level.

Physical health is critical for overall well-being, and can be affected by:

- Lifestyle: diet, level of physical activity, and behaviour (for instance, smoking);
- Human biology: a persons genetics and physiology may make it easier or harder to achieve good physical health;
- Environment: our surroundings and exposure to factors such as sunlight or toxic substances;
- Healthcare service: good healthcare can help prevent illness, as well as detect and treat illness.

Pivotal study

A pivotal study is normally a Phase III study of a new intervention which is designed to provide the necessary data for a decision by a regulatory agency.

For example, the European Medicines Agency (EMA) requires specific safety and efficacy information about new medicines before it can issue a marketing authorisation. A pivotal study will be conducted to Good Clinical Practice standards. It will generally be randomised and controlled (an RCT). It will be of adequate size and, whenever possible, double-blind.

Placebo

In clinical trials, a placebo is a medicine that contains no active ingredients. Placebos have no known medical effects.

The placebo effect is a benefit or side effect perceived by patients taking a placebo, despite the fact that no medicine is involved.

Placebo-controlled

A placebo-controlled trial is one in which a new medicine is tested against a placebo - a medicine that contains no active ingredients.

In placebo-controlled trials, people are assigned to a group (treatment arm) that receives the medicine, or a group that receives the placebo. This is one way to improve the chances that any benefit experienced by the treatment group receiving the medicine is due to the active ingredient in that medicine rather than some other factor.

Plasma

Plasma is the fluid part of blood. It contains cells, gases, proteins, enzymes, etc. Unlike blood, plasma is yellow.

Population

A population is a group of people who share a common trait. For example, they might have a certain disease of interest to researchers, have the same educational background or type of job, or they might live in a particular region.

Post authorisation safety study

A post authorisation safety study is a study carried out after a medicine has been given a marketing authorisation. Its purpose is to obtain further safety information or to assess how well risk-management measures are working. The information from a post authorisation safety study is used in regulatory decision making.

A post authorisation safety study might be a clinical trial or a non-interventional study, and can be created voluntarily by the MAH, or can be required by the regulator (imposed). The Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA) is responsible for assessing the protocols of imposed studies and for assessing the studies results. The EMA publishes the protocols and abstracts of the final study reports online.

Post marketing

Post marketing refers to the period after a medicine has been granted marketing authorisation and is available for general use.

Post-authorisation efficacy study

A post-authorisation efficacy study (PAES) may be voluntary or imposed by regulatory authorities. Post-authorisation efficacy studies take place after marketing authorisation is granted and the medicine is in general use. They are Phase IV studies, intended to complement efficacy data that are available at the time of the initial authorisation, and gather long-term data about how well the medicine works when used widely.

Post-marketing surveillance study

A post-marketing surveillance study (PMS study), also known as a Phase IV study, may be voluntary or imposed by the regulatory authorities. They are conducted after marketing authorisation is granted and the medicine is in general use. Post-marketing surveillance studies collect additional information about side-effects and safety, long-term risks and benefits, and/or how well the medicine works when it is used widely.

Potential risk

An unexpected event for which there is suspicion of an association with a medicinal product, but where this association has not been confirmed. Some examples are:

- toxicological findings seen in non-clinical safety studies which have not been observed in clinical studies;
- adverse events observed in clinical trials or epidemiological studies for which the difference compared with the control group raises a suspicion of an association, but is not large enough to suggest a causal relationship;
- a signal arising from a spontaneous adverse reaction reporting system;
- an event associated with other active substances within the same class or which could be expected to occur based on the similar properties of the medicinal product.

Precursor

A substance or cellular component from which another substance or cellular component is formed.

Predictive genetic test

A predictive genetic test is a genetic test in a person without symptoms to predict future risk of disease. This testing allows early identification of individuals at risk of a specific condition, which can lead to reduced risk through targeted screening and prevention. For example, a woman who is found to have a BRCA1 or BRCA2 gene is at increased risk of breast cancer. She might be offered regular breast screening, or even preventative surgery, to help reduce her risk.

The value of a predictive test depends on the nature of the disease for which testing is being carried out, how effective treatment is, and the cost and efficacy of screening and surveillance measures.

Predictive Medicine

Predictive medicine is a field of medicine that predicts the probability of disease. When an individual is predicted to have a high risk of a disease, preventive measures can be started in order to either prevent the disease altogether or significantly decrease its impact upon the patient. Preventive measures might be lifestyle modifications and/or increased monitoring by healthcare professionals.

Predictive medicine changes medicine from being reactive to being proactive, and has the potential to extend healthy lifetimes and to prevent disease. As yet it is not possible to predict with 100% certainty that a specific disease will occur. Predictive genetic testing is one of the key approaches in predictive medicine.

Predisposed

Someone who is predisposed to a disease is more likely than other people to develop the disease in the future.

For example, someone who is genetically predisposed to develop Alzheimers has a genetic makeup that increases their risk of developing this disease. A predisposition will not in itself cause the disease, but the disease may eventually be triggered by particular environmental or lifestyle factors, such as tobacco smoking or diet. Genetic testing is able to identify individuals who are genetically predisposed to certain diseases.

Prevalence

Prevalence is the proportion of a population found to have a condition (typically a disease or a risk factor such as smoking). It is calculated by comparing the number of people found to have the condition with the total number of people studied, and is usually expressed as a fraction (for example, 1/3), as a percentage (%) or as the number of cases per 10,000 or 100,000 people.

Prevalence can be measured at a particular point in time (point prevalence), or over a specified period such as a year (period prevalence).

Probability

Probability is the measure of the likelihood that a particular event will occur.

Probability is quantified as a number between 0 and 1 (where 0 indicates impossibility and 1 indicates certainty). The higher the probability of an event, the more certain we are that the event will occur. A simple example is the toss of a fair (unbiased) coin. Since the two outcomes are equally probable, the probability of heads is equal to the probability of tails. Therefore, the probability of either heads or tails is 1/2 (or 50%).

Proof of concept

A proof of concept (POC) trial is one type of trial carried out early in the clinical development phase of a medicine (in humans). Phase II trials usually begin with a proof of concept trial, which aims to show that the medicine interacts with its intended target and affects the disease in question.

Protocol

The protocol of a clinical trial is a document that contains:

- The objectives (aims) of the trial
- The trial design, including:
    - How participants will be selected;
    - How many participants are needed;
    - What measurements and endpoints will be used; **and**
    - How bias will be minimised
- How the safety of people taking part, and the privacy of their data, will be ensured
- How the data will be analysed
- How the study will be reported

The protocol is of critical importance to the conduct of a clinical trial; it is referred to frequently throughout the trial and the medicines development process as a whole.

Public health impact

An examination of how a health intervention (e.g. treatment, procedure, policy, etc.) might have broader implications for the health of a population. For example, a new therapy to treat HIV/AIDS may reduce the rate of HIV transmission within a community.

Publication bias

Publication bias occurs when one type of study result is more likely to be published than another.

For example, publishing results of studies that show a new treatment provides significant benefits, but not always publishing studies that show less or no benefit, will lead to publication bias. The effect is to exaggerate the benefit of the new treatment.

Methods exist to help address publication bias. For example, there are public databases where clinical trials can be registered before they begin. Thus, all the registered trials are known, including those that eventually demonstrate no significant benefit from the study treatment. Researchers are encouraged to register their trials because, for example, certain high-profile medical journals insist that they will only publish trials previously registered on a public database.

Qualitative Study

Qualitative studies are based on collecting information that describes peoples perspectives and motivations. Unlike quantitative studies, they do not try to quantify anything or use statistics.

A qualitative study might use focus groups, or interviews or observation, or a combination of methods. Sample sizes (the number of people recruited to take part) are more difficult to predict, and are often smaller than in quantitative studies. Qualitative researchers will often analyse their data as they go along, and stop looking for new people to take part when no new insights are being found.

Qualitative researchers do not assume that they know what the important issues are. Often it is not until the research is underway that the real issues are identified. Therefore, qualitative methods are general designed to give participants the freedom to raise issues that are important to them. For example, topic guides will be developed for interviews rather than tightly defined questionnaires.

Qualitative methods are often used in combination with other methods to provide rich and comprehensive data sets.

Quality Control

Quality Control (QC) is part of the system of ensuring high standards during research, trials and production for medicines. Each step of medicines development and production is managed under a Quality Management (QM) system.

The standards required are known as the Quality Assurance (QA) system, whereas QC is the method used to ensure the standards are met at each step.

Quality management for clinical research is known as Good Clinical Practice (GCP).

Quality of life

Quality of Life (QoL) is a measure in health economics. It expresses the effect of factors such as symptoms, pain, psychological health, and wellbeing on peoples lives. Health-related quality of life (HRQoL) measures are used to calculate the likely impact of treatments on the lives of patients.

Quality-adjusted life year

The quality-adjusted life year (QALY) is a measure in health economics. It expresses the additional number of years which a person lives as a result of receiving a treatment, and takes into account the quality of life of those years. It does this by measuring how important various factors are to patients, such as symptoms, pain, and psychological health.

The calculation of QALYs is a common approach used by health technology assessment (HTA) bodies, which advise about the usefulness of treatments and, in some countries, about whether treatments should be funded by (for example) government health departments.

Quantitative study

A quantitative study aims to measure and quantify, and uses statistical methods to analyse data. Unlike qualitative studies, they do not collect information about peoples perspectives and motivations.

Quasi-randomised trial

A quasi-randomised trial is one in which participants are allocated to different arms of the trial (to receive the study medicine, or placebo, for example) using a method of allocation that is not truly random.

Allocation might be based on date of birth, medical record number, or the order in which people were recruited (for example, every other person might be allocated to the placebo group).

With quasi-randomisation there is a greater risk that the investigator will be aware of which participant is in which group. There is therefore a risk of selection bias.

Randomisation

Randomisation is a method of allocating or selecting without using any system. It is purely random. In clinical trials, participants are generally allocated to different arms of the trial (for example, to receive the study medicine or the placebo) randomly. This is a key part of the randomised controlled trial (RCT).

Randomisation in clinical trials means that each participant has an equal chance of being in any of the arms of the trial. It is an important method to reduce the risk of bias in the outcomes of the trial.

Randomised clinical trial

A randomised clinical trial is one that uses randomisation when allocating people to different arms of the study. For example, in a trial comparing a new medicine with a placebo, each person has an equal chance of being allocated to the medicine or to the placebo group.

Randomised controlled trial

A randomised controlled trial is a trial in which people are allocated at random (by chance alone) to receive one of several clinical interventions such as a new medicine. One of these interventions is the control group, for example a placebo may be given, no intervention at all, or the current best treatment available. This study is one of the simplest and most powerful tools in clinical research.

Randomised participants

Participants in a trial who have been randomly (by chance) assigned to one intervention arm or another of that trial. Practical considerations, such as missing data over time, may lead to some participants not being included in the final analysis.

Rare disease

A rare disease, also referred to as an orphan disease, is any disease that affects a small percentage of the population. Rare disease are commonly defined as life-threatening or chronically debilitating diseases which are of such low prevalence (fewer than 1 in 2,000 people) that special combined efforts are needed to address them. Diseases that are statistically rare, but not also life-threatening, chronically debilitating, or inadequately treated, are excluded from this definition. A disease may be considered rare in one part of the world, or in a particular group of people, but still be common in another.

Most rare diseases are genetic so that most people show symptoms from childhood (although some rare diseases only become apparent later in life).

Recruitment

Recruitment is the process used by investigators to enrol people (participants) into a clinical study. Recruitment is based on the inclusion and exclusion criteria that are documented in the study protocol.

Recurrence

Recurrence is the return of a sign, symptom, or disease after some time when the signs or symptoms could not be detected. It is applied to the return of symptoms of an incurable disease. For example, the reappearance of cancer cells at the same site as the original tumour, or in another location. The risk of a recurrence depends on many factors, including the type of illness and type and/or time of treatment.

Reference medicine

When talking about biosimilar and generic medicines, a reference medicine is the existing medicine already on the market that biosimilar and generic medicines are developed to be similar to or copies of, respectively.

Regulatory affairs

Regulatory affairs is a relatively new profession which developed from the desire of governments to protect public health by controlling the safety and efficacy of products in areas including human medicines, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines. The Regulatory Affairs departments of pharmaceutical companies ensure that their companies comply with the regulations and laws governing medicinal products or medical devices. They are the key interface between the company and the regulatory authorities.

Reimbursement

In clinical research, is the economic compensation for legitimate expenses incurred by a participant taking part in a specific research project.

Relative clinical effectiveness

It can be defined as the extent to which an intervention does more good than harm compared to one or more alternative interventions for achieving the desired results, when provided under the usual circumstances of health care practice.

Relative efficacy

It is the extent to which an intervention does more good than harm compared to one or more alternative interventions, when provided under ideal circumstances.

Reliability

The reliability of a measurement or tool is how consistent it is. A reliable measurement or tool will give the same result when repeated at random in the same patient or sample. In clinical trials, reliability is an important consideration in the choice of primary outcome measures (such as an improvement in certain symptoms). The reliability of measures should be formally assessed during the design of clinical trials.

Reliability is different to validity, which is the extent to which a measurement measures what it is supposed to.

Remission

Remission is a temporary end (or significant reduction) in the signs and symptoms of an incurable disease. A disease is said to be incurable if there is always a chance that the patient will become ill again, no matter how long they have been in remission.

In cancer, the term in remission is often used. Partial remission means the cancer is still detectable, but tumours or smaller, or - as in leukaemia - when there is less cancer throughout the body. Complete remission means that cancer cannot be detected using tests or scans - but because there is always the chance that cancer cells are still present, patients are said to be in remission rather than cured.

Risk

Risk is the probability of harm or injury occurring as a result of using a treatment in clinical practice or as part of a research study. The harm or injury may be physical, but can also be psychological, social, or economic. Risks may include experiencing side effects of the treatment, or taking a medication that is not as effective as the standard treatment (during a trial). In a trial, a new treatment may have side effects or risks that researchers do not expect. This is more likely in the early stages of clinical trials.

No clinical trial is risk free. Participants should be aware of both the benefits and the risks before they make a decision about whether or not to take part (see informed consent).

Risk assessment

Risk assessment is one of the three pillars of risk management (together with safety specifications and the risk minimisation plan). It contains both routine and additional pharmacovigilance activities to characterise the safety profile of the medicinal product including what is known and not known. It does NOT include actions intended to reduce, prevent or mitigate risks.

Risk Evaluation and Mitigation Strategy (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is used in the United States, and is similar to the Risk Management Plan (RMP) in the EU.

Risk factor

A risk factor is a characteristic, condition or habit that increases a persons chances to develop a particular disease or injury, for example, physical inactivity may, over time, contribute to weight gain, high blood pressure and high cholesterol levels. Risk factors include:

- behavioural (poor diet, smoking, alcohol consumption),
- biomedical (high weight, high blood pressure),
- environmental (social, economic, cultural),
- genetic (chromosomal abnormalities),
- demographic (age, gender, ethnicity).

Risk management

Risk management is a process for identifying, assessing, prioritising, and taking the appropriate action to mitigate a risk. The objective of risk management is to continuously try to ensure that the benefits of a particular medicinal product (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.

Risk management plan

A risk management plan provides a detailed description of the activities and interventions in place to prevent or minimise risks of using a medicine. Risk management plans outline how more knowledge about the safety and efficacy of a medicine will be generated, what are the risk factors for developing side effects, and how risk-minimisation measures will be monitored.

Risk management plans must be submitted by companies at the same time they apply for marketing authorisation in the European Union, although they must be continually updated and revised throughout the medicines lifetime. Risk management plans can also be requested by the EMA at other times, or whenever there is concern that a risk may be affecting the balance of benefits and risks for a particular medicine.

Risk minimisation measures

These are public health interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. Risk minimisation measures aim to optimise the safe and effective use of a medicinal product throughout its life cycle. Planning and implementing risk minimisation measures and assessing their effectiveness are key elements of risk management. Routine risk minimisation involves the use of the tools such as the Summary of Product Characteristics (SmPC), the package leaflet, the labelling, the pack size and design, and the legal (prescription) status of the product.

The majority of safety concerns may be adequately addressed by routine risk minimisation measures, but for some risks however, additional risk minimisation measures are necessary to manage risk and/or improve the benefit-risk balance of a medicinal product.

Sample size

In a clinical trial, the sample size is the number of patients or observations made. There must be enough patients or observations so that differences between groups within the trial can be detected. An estimate of sample size is required and must be specified in the study protocol before recruitment starts. It is also necessary to control the probability with which a real effect can be identified as statistically significant. Too few patients or observations will mean that real effects might not be detected, or they will be detected but at a level that is statistically insignificant (a Type II error, which is directly proportional to sample size). It is just as true that it is unjustified for a medicine to be tested on too many patients.

Scale-up

In pharmaceutical development, scale-up refers to the transition of a manufacturing process from lab scale (typically milligrams/grams) to plant-scale or commercial scale (typically kilograms/tonnes).

Scientific Advice Working Party (SAWP)

The Scientific Advice Working Party (SAWP) within the European Medicines Agency (EMA) provides scientific advice and protocol assistance to companies developing medicines. The SAWP was established by the EMAs Committee for Medicinal Products for Human Use (CHMP).

It is a multi-disciplinary group with expertise in non-clinical safety, pharmacokinetics, methodology and statistics, and in therapeutic fields for which there are frequent requests or other specific fields such as cardiology, oncology, diabetes, neurodegenerative disorders and infectious diseases including human-immunodeficiency-virus (HIV) infection. Membership includes representatives from the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO), and the Committee for Advanced Therapies (CAT).

The SAWP develops integrated views on quality relating to the development of medicines; non-clinical and clinical safety and efficacy relating to the development of medicines; and the significant benefit of orphan medicines.

Scientific Advisory Group (SAG)

Scientific advisory groups (SAG) at the European Medicines Agency (EMA) provide independent recommendations on scientific /technical matters related to medicinal products under evaluation at the EMA, or any other relevant scientific issue. Scientific advisory groups are created by the EMAs Committee for Medicinal Products for Human Use (CHMP). They consist of experts selected according to the particular expertise required.

Sensitivity

Sensitivity (of an assay or test) is the ability of an experiment or trial to detect a difference for instance, between two groups of participants receiving different medicines in a clinical trial.

Serious adverse event

An adverse event (AE) is called serious if it:

- results in death
- is life-threatening (at risk of death at the time of the adverse event, not an event which could hypothetically have caused death if it were more severe)
- requires hospitalisation or extension of existing inpatients? hospitalisation
- results in a persistent or significate disability or incapacity, or
- is a congenital anomaly or birth defect

Other events such as those requiring emergency intervention to prevent one of the serious outcomes described above might also be reported as a serious adverse event.

Serious adverse reaction

An adverse drug reaction (ADR) is called serious if at any dose it:

- results in death,
- is life-threatening (at risk of death at the time of the adverse event, not an event which could hypothetically have caused death if it were more severe),
- requires hospitalisation or extension of existing inpatients hospitalisation,
- results in a persistent or significant disability or incapacity, or
- is a congenital anomaly or birth defect.

Side Effect

A side effect, or adverse reaction, is an unintended response to a medication. Side effects are generally regarded as being harmful, and may occur after a single dose or prolonged administration. They might result from the normal use of a medicine, or from the use of a medicine in a way unintended by the marketing authorisation holder (MAH) such as taking an overdose or from the combination of two or more medicines being taken at once.

Significance

In a clinical trial, the significance is a description of how meaningful (valid) a trial result is. When evaluating the validity of a study, one must consider both the clinical and statistical significance of the findings. A study that claims clinical relevance may lack sufficient statistical significance to make a meaningful statement. Conversely, a study that shows a statistically significant difference in two treatment options may lack clinical relevance (if, for instance, an observed effect is very small but highly consistent).

Significance level

The significance level (or _ level) is a threshold that determines whether a study result can be considered statistically significant after performing the planned statistical tests. The significance level is most often set to 5% (or 0.05), although other levels may be used depending on the study. This represents the probability of rejecting the null hypothesis when it is true. For example, a significance level of 0.05 indicates a 5% risk of concluding that a difference between the study results and the null hypothesis exists when there is no actual difference.

The significance level must be stated in the trial protocol as part of the statistics section. The probability of a result being due to chance rather than due to a medicine or other intervention being studied, if the null hypothesis is true (that is, if there is really no true difference), is known as the p-value. A result is then said to be statistically significant if it yields a p-value equal to or less than the significance level and thus will not be considered a chance occurrence. This is generally written as $p = 0.05$.

Soft Endpoint

The endpoint in a clinical trial is an event such as occurrence of a disease, or symptom, or a particular laboratory result. Once someone reaches the endpoint, they are generally excluded from further research in the trial.

A soft endpoint is a subjective measure. For example, it is common to measure quality of life as an endpoint in Phase III trials, with patients asked specific questions about the impact of their disease and/or treatment.

In contrast, a hard endpoint is an endpoint that is well defined and can be measured objectively. For example in cancer research, the endpoint in a trial might be related to response to treatment (such as shrinkage of a tumour).

The endpoints used in a trial must be defined and documented as part of the trial design.

Solubility

The ability of a substance (solute) to permanently dissolve in liquid to form a homogeneous solution.

Specificity

Specificity (of an assay or test) is the ability of an experiment or trial to correctly detect only the particular effect being studied for instance, a difference in symptoms between two groups of participants receiving different medicines in a clinical trial. If a trial is not specific enough, it will give a false positive result (Type I error).

Stability

Stability is the ability of a substance to remain unchanged. Changes may occur due to the environment that the substance is in, e.g. being exposed to sunlight or water, or being in the body. Changes may also occur due to chemical and biological processes found inside the substance.

Standard deviation

The standard deviation is a measure of the amount of variation within a data set. If all values in a data set are very close together, the standard deviation will be close to zero. In such cases, the data points will all lie close to the mean (average). A high standard deviation indicates that the values are much more spread out.

The standard deviation is normally included when clinical trial results are reported because it provides a (rough) guide to statistical significance. Take, for example, a clinical trial in which the observed symptom reduction is greater than one would expect if the medicine had no effect. The difference (between the observed result and what one would expect if the medicine had no effect) would generally have to be greater than two times the standard deviation to be regarded as statistically significant.

Stem cell therapy

Stem cell therapy, also known as regenerative medicine, is the use of stem cells to treat or prevent a disease or condition. Stem cells grown in a lab are manipulated to specialise into specific types of cells, such as heart muscle cells, blood cells or nerve cells. The specialised cells can then be implanted into a person. For example, if the person has heart disease, the cells could be injected into the damaged heart muscle. The healthy transplanted heart cells could then contribute to repairing defective heart muscle.

Stem cells

Stem cells are undifferentiated (unspecialised) cells that can transform into specialised cells and can divide to produce more stem cells. They have the potential to develop into many different cell types in the body during early life and growth. In addition, in many tissues they serve as an internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. There are two types of stem cells: Embryonic stem cells, found in the early stage of embryonic development, can differentiate into all the specialised cells of the body, such as muscle cells, red blood cells, and nerve cells. Adult stem cells, which are found in some adult tissues, can act as a repair system for the body.

Stratification

In clinical trials, stratification is the separation of patients or the analysis of results based on something other than the treatment given.

Stratification has two different meanings. In its first meaning, it describes the natural distribution of patients into subgroups. For instance, patients may be stratified by age, disease severity, or biomarkers.

In its second meaning, stratification controls the random allocation of people to the different groups in a trial. Stratified randomisation is used to ensure that equal numbers of participants with a characteristic thought to affect response to the intervention will be allocated to each group in the trial.

Stratified medicine

Stratified medicine is based on the identification of subgroups of patients that differ in their mechanisms of disease, their susceptibility to a particular disease, or in their response to a medicine. The aim of stratified medicine is to offer the treatment that is most likely to give benefit, or to avoid an adverse reaction. Personalised medicine takes this approach a step further by using targeted medicines and also taking information such as the patients genotype and lifestyle into account when deciding on the best treatment.

Subcutaneous

This is the administration of a medicine into the layer of skin directly below the dermis and epidermis (the top layers of skin). Subcutaneous tissue has few blood vessels and so medicines administered here are for slow, sustained rates of absorption. An example is a local anaesthetic injected before suturing.

Sublingual

A route of medicine administration in which the medicine is placed under the tongue. These medications can come in the form of tablets, films, or sprays. It is an extremely fast pharmacological route of absorption, as medicines diffuse rapidly into the blood through tissues under the tongue. This is especially effective in an emergency when the medication needs to work immediately like during a heart attack. Another advantage is that the medicine does not go through the digestive system, so it is not metabolised through the liver, and thus a lower dose can be used.

Subpopulation

Subpopulations are groups within a population. The population might be defined by, for example, the presence of a certain disease of interest to researchers. A subpopulation within that will have additional traits, such as disease severity, or failure of previous treatments, or specific genetic traits, or belonging to a certain age group that are also of interest. Subpopulations are identified in this way to allow statistical analysis with respect to the additional traits of interest.

Summary of product characteristics

The Summary of Product Characteristics (SmPC) is a document approved as part of the marketing authorisation of each medicine. It is aimed at healthcare professionals and includes information such as:

- How to use the medicine;
- What the medicine should be used to treat (therapeutic indications);
- Dose;
- Method of administration;
- In what conditions the medicine should not be used (contraindications);
- Special warnings;
- The medicines mechanism of action; **and**
- Any undesirable effects.

The SmPC contains more detail than the Package Leaflet (PL).

Surrogate endpoint

The endpoint in a clinical trial is an event such as the occurrence of a disease, or symptom, or a particular laboratory result. Once someone reaches the endpoint, they are generally excluded from further research in the trial.

A surrogate endpoint (or marker) is a measure which in itself is not the outcome that the study treatment aims to elicit. For example, blood pressure is used as a surrogate endpoint in trials because it is a risk factor for heart attacks and strokes even though in itself blood pressure might not be important for patients.

Surrogate endpoints are useful if it would take a very long time for clinical endpoints to appear. Surrogate endpoints must be proven to be valid markers of clinical endpoints when they are used in clinical trials.

Suspected unexpected serious adverse reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR), is a serious adverse reaction (SAR) for which a reasonable causal relationship with the medicine use is suspected but not confirmed. Unexpected in this context means not consistent with the applicable product information (e.g. investigators brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

Target patient population

Refers to the patients the medicine is intended for.

Target product profile

A target product profile is a document that describes the features of a product (such as a medicine) that a company is planning or developing. The document can include a wide range of information such as dosage, how the product will be administered (for example this could be a patient taking a medicine by mouth, or a hospital nurse giving the medicine as an injection), formulation, clinical studies, adverse reactions (unwanted harmful effects) and contraindications (situations when the product should not be used).

The target product profile is written by the company developing the treatment, and if it is begun early it can help keep their development work properly focused on the end goal. A target product profile can also be used as a basis for discussions between the company and those regulatory authorities that will assess the product for release to market.

Targeted medicine

These are medicines designed in a manner that focuses the activity of the medication in certain parts of the body. The goal of a targeted medicine is to increase the length of time that the medicine interacts with the diseased tissue in a specific area of the body and spares other parts (e.g. affecting tumour cells rather than adjacent healthy cells). The advantages of a targeted release system are the reduction in the frequency of the dosages taken by the patient, having a more consistent effect of the medicine, reduction of side effects, and reduced fluctuation in medicine levels in the body.

Therapeutic alternatives

Therapeutic alternatives are medicines that are chemically different from the one prescribed (used) but which have the same clinical effect. Therapeutic alternatives are not to be confused with generics.

Therapeutic indication

Therapeutic indications are a description of the disease to be treated with a medicine, and the population for which the medicine is intended. They include the specifics about the disease, and restrictions to the patient population such as age, and whether the medicine is intended for symptom relief, cure or prevention, or whether it is for diagnostic use only.

Example statements from therapeutic indications:

- Symptomatic treatment of mild to moderately severe Alzheimers disease.
- Active substance X 40 mg is indicated for the prevention of post-operative nausea and vomiting (PONV) in adults.

Therapeutic indications must be clearly and concisely stated within the summary of product characteristics (SmPC) document that each medicine requires in the EU.

Time-to-event endpoint

A time-to-event endpoint is the time taken until a pre-defined event takes place, once groups in a trial start to receive treatment or placebo. There are several kinds of time-to-event endpoints. For example, time-to-progression (TTP) is the time between randomisation of people to groups within a trial, and disease progression. Disease progression in this case must be defined, and it must be specific and measurable. For example, the growth of a particular tumour type by a minimum amount may be used as an indicator of disease progression.

Tolerability

The tolerability of the medicinal product represents the degree to which adverse effects can be tolerated or accepted by a patient.

Toxicity

Toxicity is the degree to which a chemical or biological substance can damage a living organism. It can refer to harm to specific organs, tissues or cells, or to the whole organism.

Medicines development is a step-by-step process involving the evaluation of both animal and human safety information. Non-clinical safety studies (before human testing) should be able to identify potential toxic effects that might occur under the conditions of the later clinical trial.

Treatment emergent adverse event

Treatment emergent adverse events (TEAE) are undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment.

In medicines development terminology, an adverse event (AE) is any undesirable event that occurs after a participant officially consents to take part in a trial (and could occur before treatment begins). An adverse event may or may not be associated with the medicine under investigation, but must be documented because it happened during the trial period.

A treatment emergent adverse event (TEAE) is an adverse event that occurs only once treatment has started.

Treatment group

In a clinical trial, the treatment group (as opposed to the control group) usually refers to the group of participants that receives the treatment under investigation. The treatment group is also known as the treatment arm.

Trial arm

A trial arm is a group of participants that receives the same interventions, or no intervention, according to the study protocol. Many randomised trials have two arms, but some may have three or even more. This is decided before the trial begins.

Trials with several arms (multi-arm) allow more than one treatment to be tested at once, and can reduce the costs and time needed during clinical development. Multi-arm, multi-stage (MAMS) trials take this idea a step further and allow the recruitment of participants in a particular arm to be stopped partway through if that treatment is not producing satisfactory results. MAMS can also allow for new treatments to be added to the trial as they become ready for testing.

Type I Error

Type I Error occurs in statistical hypothesis testing when a null hypothesis, which is actually true, is incorrectly rejected. Type I errors are also known as false positives; they are the detection of a positive effect where no effect actually exists.

As a stark example, Type I errors could kill a patient - for instance, if a study incorrectly found that the standard of care was not better than the new treatment, and consequently the new treatment was given to patients, the results may be catastrophic.

Type I errors cannot be completely avoided, but researchers should decide on an acceptable level of risk of Type I error when designing clinical trials. A number of statistical methods can be used to control the Type I error rate. The methods to be sued in a clinical trial should be detailed in the study protocol or the statistical analysis plan for that trial.

Type II Error

Type II Error occurs in statistical hypothesis testing when the null hypothesis is incorrectly accepted. Type II errors are also known as false negatives; they are the failure to detect a positive effect where the effect does exist.

Type II errors mean that potentially valuable research goes to waste. As no positive effect is detected, research may be halted. This research may have been useful, but as no further study takes place, no harm is done to patients.

Type II errors cannot be completely avoided, but researchers should decide on an acceptable level of risk of Type II error when designing clinical trials. To reduce the risk of Type II errors to acceptable levels, the power or sample size (the number of participants in a study) can be increased.

Unexpected Adverse Reaction

An unexpected adverse reaction is a harmful and unintended response to a medication which is not consistent with applicable product information or characteristics of the medicinal product.

Vulnerable participants or populations

Vulnerable participants or populations are individuals or groups of individuals who are unable to give informed consent to take part in a clinical trial, such as children or people affected by mental health conditions, or who may come under pressure from others to take part. It also includes people whose willingness to volunteer in a clinical trial may be unduly influenced by their expectations of taking part.

If a trial is to include people from vulnerable populations, special attention should be paid to protecting their well-being, both by the investigators and the ethics committee that reviews the trial protocol.

Wash out period

In a clinical trial, this refers to a break in ongoing treatment. It is quite often used in crossover trials where a set period is defined before switching to a new medicine. In this period the levels of the previous medicine in the body and the effects should be reduced to zero.