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Drug discovery & clinical trials: Login passwords to new life

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Abstract

In the fields of medicine, biotechnology and pharmacology, drug discovery is the process by which new candidate medications are discovered. Historically, drugs were discovered by identifying the active ingredient from traditional remedies or by serendipitous discovery, as with penicillin. More recently, chemical libraries of synthetic small molecules, natural products or extracts were screened in intact cells or whole organisms to identify substances that had a desirable therapeutic effect in a process known as classical pharmacology. After sequencing of the human genome allowed rapid cloning and synthesis of large quantities of purified proteins, it has become common practice to use high throughput screening of large compounds libraries against isolated biological targets which are hypothesized to be disease–modifying in a process known as reverse pharmacology. Hits from these screens are then tested in cells and then in animals for efficacy. Depending on product type and development stage, investigators initially enrol volunteers or patients into small pilot studies, and subsequently conduct progressively larger scale comparative studies. Clinical trials can vary in size and cost, and they can involve a single research centre or multiple centres, in one country or in multiple countries. Clinical study design aims to ensure the scientific validity and reproducibility of the results.

Costs for clinical trials can range into the billions of dollars per approved drug. The sponsor may be a governmental organization or a pharmaceutical, biotechnology or medical device company. Certain functions necessary to the trial, such as monitoring and lab work, may be managed by an outsourced partner, such as a contract research organization or a central laboratory. Only 10 percent of all drugs started in human clinical trials become approved drugs.

Keywords: Drug Discovery; Clinical Trial; Drug Screening; Drug Designing

1. Introduction

Modern drug discovery involves the identification of screening hits, medicinal chemistry and optimization of those hits to increase the affinity, selectivity (to reduce the potential of side effects), efficacy/potency, metabolic stability (to

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increase the half–life), and oral bioavailability. Once a compound that fulfills all of these requirements has been identified, the process of drug development can continue. If successful, clinical trials are developed.[1]

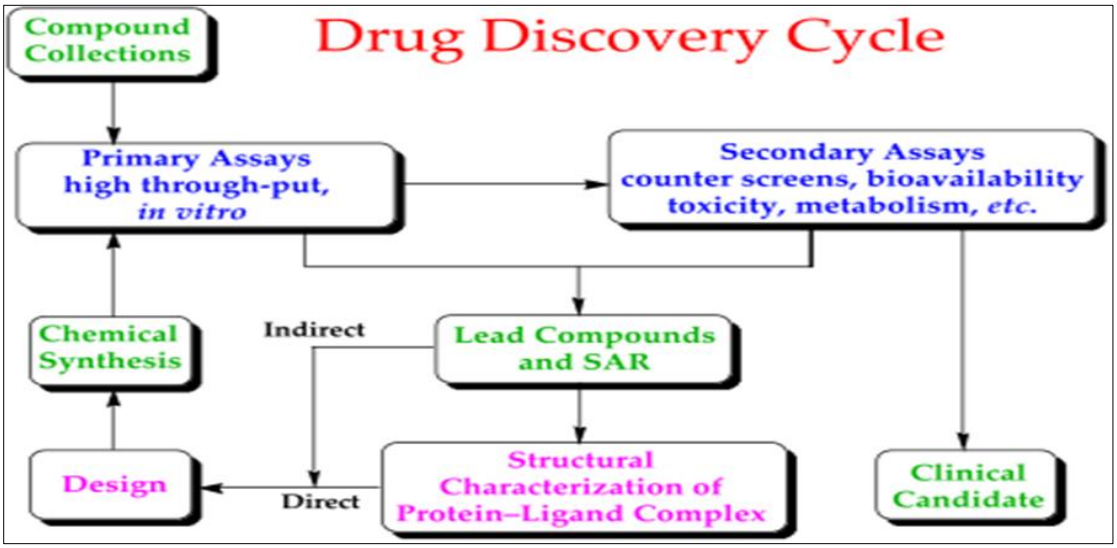

Figure 1 Drug Discovery Cycle

Drug is a substance obtained from either synthetic source, semisynthetic source and natural source [plants (flora), animals (fauna), mineral source and marine source] having definite structural framework of low range of toxicity [therapeutic index] which has capability to fit on bio receptor platform [macromolecular bed] having controlling capacity to check the biochemical malfunction *in–vivo*. Modern drug discovery is thus usually a capital–intensive process that involves large investments by pharmaceutical industry corporations as well as national governments (who provide grants and loan guarantees). Despite advances in technology and understanding of biological systems, drug discovery is still a lengthy, "expensive, difficult, and inefficient process" with low rate of new therapeutic discovery. In 2010, the research and development cost of each new molecular entity was about US$1.8 billion. In the 21st century, basic discovery research is funded primarily by governments and by philanthropic organizations, while late–stage development is funded primarily by pharmaceutical companies or venture capitalists. To be allowed to come to market, drugs must undergo several successful phases of clinical trials, and pass through a new drug approval process, called the New Drug Application in the United States.[2]

Discovering drugs that may be a commercial success, or a public health success, involves a complex interaction between investors, industry, academia, patent laws, regulatory exclusivity, marketing and the need to balance secrecy with communication. Meanwhile, for disorders whose rarity means that no large commercial success or public health effect can be expected, the orphan drug funding process ensures that people who experience those disorders can have some hope of pharmacotherapeutic advances.[3]

1.1. History

Pharmacy is a subject which runs on its two legs: chemistry & biology. Actually chemistry is focused on synthetic chemistry, organic chemistry, physical chemistry, inorganic chemistry, analytical chemistry, biochemistry, medicinal chemistry, computational chemistry, green chemistry, phytochemistry and biology is focused over pharmacology and drug design. The idea that the effect of a drug in the human body is mediated by specific interactions of the drug molecule with biological macromolecules, (proteins or nucleic acids in most cases) led scientists to the conclusion that individual chemicals are required for the biological activity of the drug. This made for the beginning of the modern era in pharmacology, as pure chemicals, instead of crude extracts of medicinal plants, became the standard drugs. Examples of drug compounds isolated from crude preparations are morphine, the active agent in opium, and digoxin, a heart stimulant originating from *Digitalis lanata*. Organic chemistry also led to the synthesis of many of the natural products isolated from biological sources. Historically, substances, whether crude extracts or purified chemicals, were screened for biological activity without knowledge of the biological target. Only after an active substance was identified was an effort made to identify the target. This approach is known as classical pharmacology, forward pharmacology, or phenotypic drug discovery.

Figure 2 Stalwarts of drug discovery

Later, small molecules were synthesized to specifically target a known physiological/pathological pathway, avoiding the mass screening of banks of stored compounds. This led to great success, such as the work of Gertrude Elion [January 23, 1918 – February 21, 1999; Nobel Prize in physiology/medicine: 1988] and George H. Hitchings [April 18, 1905 – February 27, 1998; Nobel Prize in physiology/medicine: 1988] on purine metabolism, the work of James Black [14 June 1924 – 22 March 2010; Nobel Prize in medicine: 1988] on beta blockers and cimetidine, and the discovery of statins by Akira Endo [born: 14 November 1933]. Another champion of the approach of developing chemical analogues of known active substances was Sir David Jack [22 February 1924 – 8 November 2011] at Allen and Hanbury's, later Glaxo, who pioneered the first inhaled selective β2–adrenergic agonist for asthma, the first inhaled steroid for asthma, ranitidine as a successor to cimetidine, and supported the development of the triptans. Gertrude Elion, working mostly with a group of fewer than 50 people on purine analogues, contributed to the discovery of the first anti–viral; the first immunosuppressant (azathioprine) that allowed human organ transplantation; the first drug to induce remission of childhood leukemia; pivotal anti–cancer treatments; an anti–malarial; an anti–bacterial; and a treatment for gout. Cloning of human proteins made possible the screening of large libraries of compounds against specific targets thought to be linked to specific diseases. This approach is known as reverse pharmacology and is the most frequently used approach today.

1.2. Targets

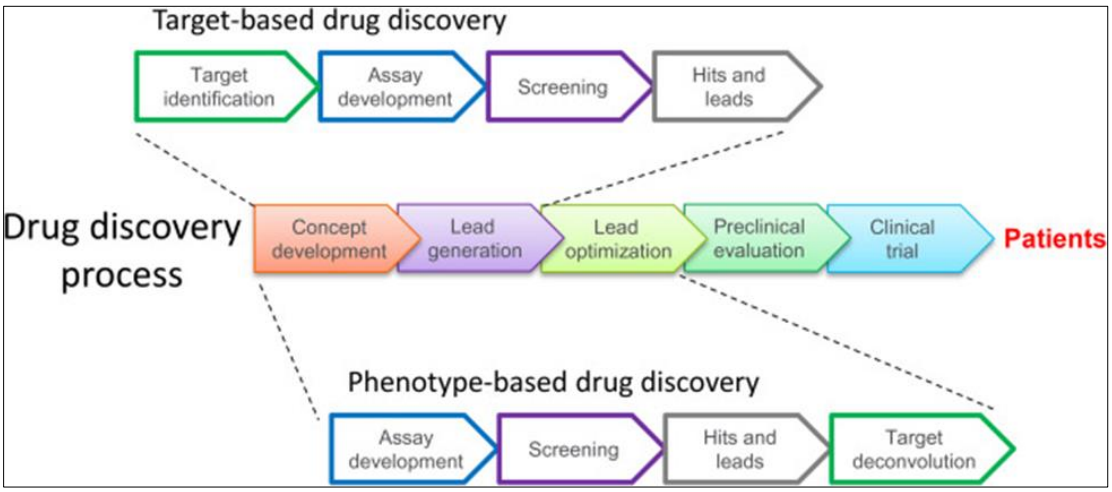

Figure 3 Drug Discovery Process

A "target" is produced within the pharmaceutical industry. Generally, the "target" is the naturally existing cellular or molecular structure involved in the pathology of interest where the drug–in–development is meant to act. However, the distinction between a "new" and "established" target can be made without a full understanding of just what a "target" is. This distinction is typically made by pharmaceutical companies engaged in the discovery and development of therapeutics. In an estimate from 2011, 435 human genome products were identified as therapeutic drug targets of FDA–approved drugs.[4] "Established targets" are those for which there is a good scientific understanding, supported by a lengthy publication history, of both how the target functions in normal physiology and how it is involved in human pathology. This does not imply that the mechanism of action of drugs that are thought to act through a particular established target is fully understood. Rather, "established" relates directly to the amount of background information available on a target, in particular functional information. In general, "new targets" are all those targets that are not

"established targets" but which have been or are the subject of drug discovery efforts. The majority of targets selected for drug discovery efforts are proteins, such as G–protein–coupled receptors (GPCRs) and protein kinases by pharmacophore modelling.

1.3. Screening and design

The process of finding a new drug against a chosen target for a particular disease usually involves high–throughput screening (HTS), wherein large libraries of chemicals are tested for their ability to modify the target. For example, if the target is a novel GPCR, compounds will be screened for their ability to inhibit or stimulate that receptor (see antagonist and agonist): if the target is a protein kinase, the chemicals will be tested for their ability to inhibit that kinase.[5] Another function of HTS is to show how selective the compounds are for the chosen target, as one wants to find a molecule which will interfere with only the chosen target, but not other, related targets. To this end, other screening runs will be made to see whether the "hits" against the chosen target will interfere with other related targets – this is the process of cross–screening. Cross–screening is useful because the more unrelated targets a compound hits, the more likely that off–target toxicity will occur with that compound once it reaches the clinic.

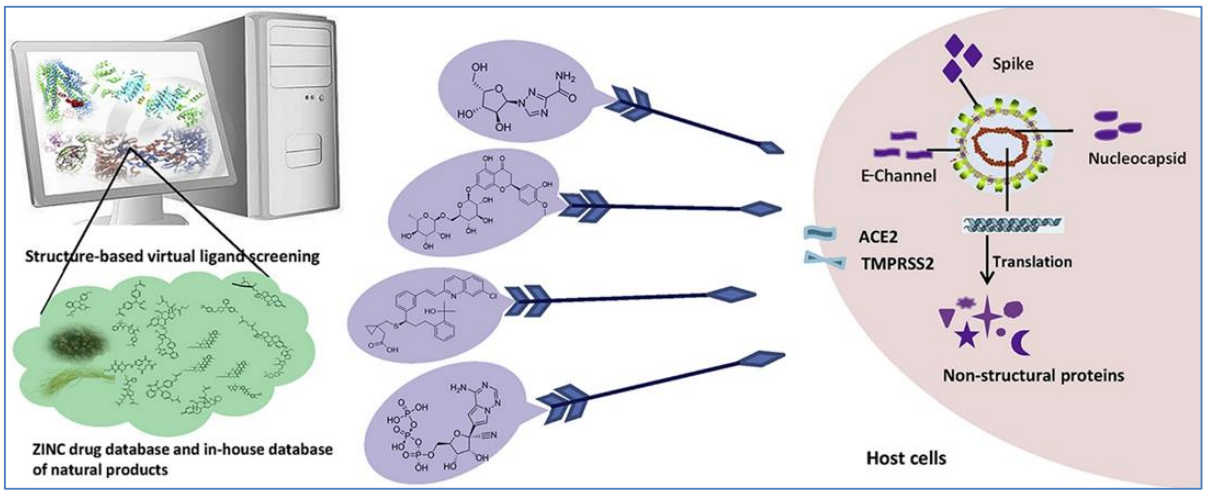

Figure 4 Screening Method of an Antiviral Drug

It is unlikely that a perfect drug candidate will emerge from these early screening runs. One of the first steps is to screen for compounds that are unlikely to be developed into drugs; for example compounds that are hits in almost every assay, classified by medicinal chemists as "pan–assay interference compounds", are removed at this stage, if they were not already removed from the chemical library. It is often observed that several compounds are found to have some degree of activity, and if these compounds share common chemical features, one or more pharmacophores can then be developed. At this point, medicinal chemists will attempt to use structure–activity relationships (SAR) to improve certain features of the lead compound:

- Increase activity against the chosen target
- Reduce activity against unrelated targets
- Improve the drug likeness or ADME properties of the molecule.

This process will require several iterative screening runs, during which, it is hoped, the properties of the new molecular entities will improve, and allow the favoured compounds to go forward to in vitro and in vivo testing for activity in the disease model of choice. Amongst the physicochemical properties associated with drug absorption include ionization (pKa), and solubility; permeability can be determined by PAMPA and Caco–2. PAMPA is attractive as an early screen due to the low consumption of drug and the low cost compared to tests such as Caco–2, gastrointestinal tract (GIT) and Blood–brain barrier (BBB) with which there is a high correlation. A range of parameters can be used to assess the quality of a compound, or a series of compounds, as proposed in the Lipinski's Rule of Five. Such parameters include calculated properties such as cLogP to estimate lipophilicity, molecular weight, polar surface area and measured properties, such as potency, in–vitro measurement of enzymatic clearance etc. Some descriptors such as ligand efficiency (LE) and lipophilic efficiency (LiPE) combine such parameters to assess drug likeness. While HTS is a commonly used method for novel drug discovery, it is not the only method. It is often possible to start from a molecule which already has some of the desired properties. Such a molecule might be extracted from a natural product or even be a drug on the market which could be improved upon (so–called "me too" drugs). Other methods, such as virtual high

throughput screening, where screening is done using computer–generated models and attempting to "dock" virtual libraries to a target, are also often used.

Another method for drug discovery is *de novo* drug design, in which a prediction is made of the sorts of chemicals that might (e.g.) fit into an active site of the target enzyme. For example, virtual screening and computer–aided drug design are often used to identify new chemical moieties that may interact with a target protein. Molecular modelling and molecular dynamics simulations can be used as a guide to improve the potency and properties of new drug leads. There is also a paradigm shift in the drug discovery community to shift away from HTS, which is expensive and may only cover limited chemical space, to the screening of smaller libraries (maximum a few thousand compounds). These include fragment–based lead discovery (FBDD) and protein–directed dynamic combinatorial chemistry. The ligands in these approaches are usually much smaller, and they bind to the target protein with weaker binding affinity than hits that are identified from HTS. Further modifications through organic synthesis into lead compounds are often required. Such modifications are often guided by protein X–ray crystallography of the protein–fragment complex. The advantages of these approaches are that they allow more efficient screening and the compound library, although small, typically covers a large chemical space when compared to HTS.

Phenotypic screens have also provided new chemical starting points in drug discovery. A variety of models have been used including yeast, zebrafish, and worms, immortalized cell lines, primary cell lines, patient–derived cell lines and whole animal models. These screens are designed to find compounds which reverse a disease phenotype such as death, protein aggregation, mutant protein expression, or cell proliferation as examples in a more holistic cell model or organism. Smaller screening sets are often used for these screens, especially when the models are expensive or time–consuming to run. In many cases, the exact mechanism of action of hits from these screens is unknown and may require extensive target deconvolution experiments to ascertain. The growth of the field of chemoproteomics has provided numerous strategies to identify drug targets in these cases. Once a lead compound series has been established with sufficient target potency and selectivity and favourable drug–like properties, one or two compounds will then be proposed for drug development. The best of these is generally called the lead compound, while the other will be designated as the "backup". These decisions are generally supported by computational modelling innovations.[6]

1.4. Nature as source

Traditionally, many drugs and other chemicals with biological activity have been discovered by studying chemicals that organisms create to affect the activity of other organisms for survival. Despite the rise of combinatorial chemistry as an integral part of lead discovery process, natural products still play a major role as starting material for drug discovery. A 2007 report found that of the 974 small molecule new chemical entities developed between 1981 and 2006, 63% were natural derived or semisynthetic derivatives of natural products. For certain therapy areas, such as antimicrobials, antineoplastics, antihypertensive and anti–inflammatory drugs, the numbers were higher. In many cases, these products have been used traditionally for many years. Natural products may be useful as a source of novel chemical structures for modern techniques of development of antibacterial therapies.

1.5. Plant–derived

Many secondary metabolites produced by plants have potential therapeutic medicinal properties. These secondary metabolites contain, bind to, and modify the function of proteins (receptors, enzymes, etc.). Consequently, plant derived natural products have often been used as the starting point for drug discovery.

Until the Renaissance, the vast majority of drugs in Western medicine were plant–derived extracts. This has resulted in a pool of information about the potential of plant species as important sources of starting materials for drug discovery. Botanical knowledge about different metabolites and hormones that are produced in different anatomical parts of the plant (e.g. roots, leaves, and flowers) are crucial for correctly identifying bioactive and pharmacological plant properties. Identifying new drugs and getting them approved for market has proved to be a stringent process due to regulations set by national drug regulatory agencies.

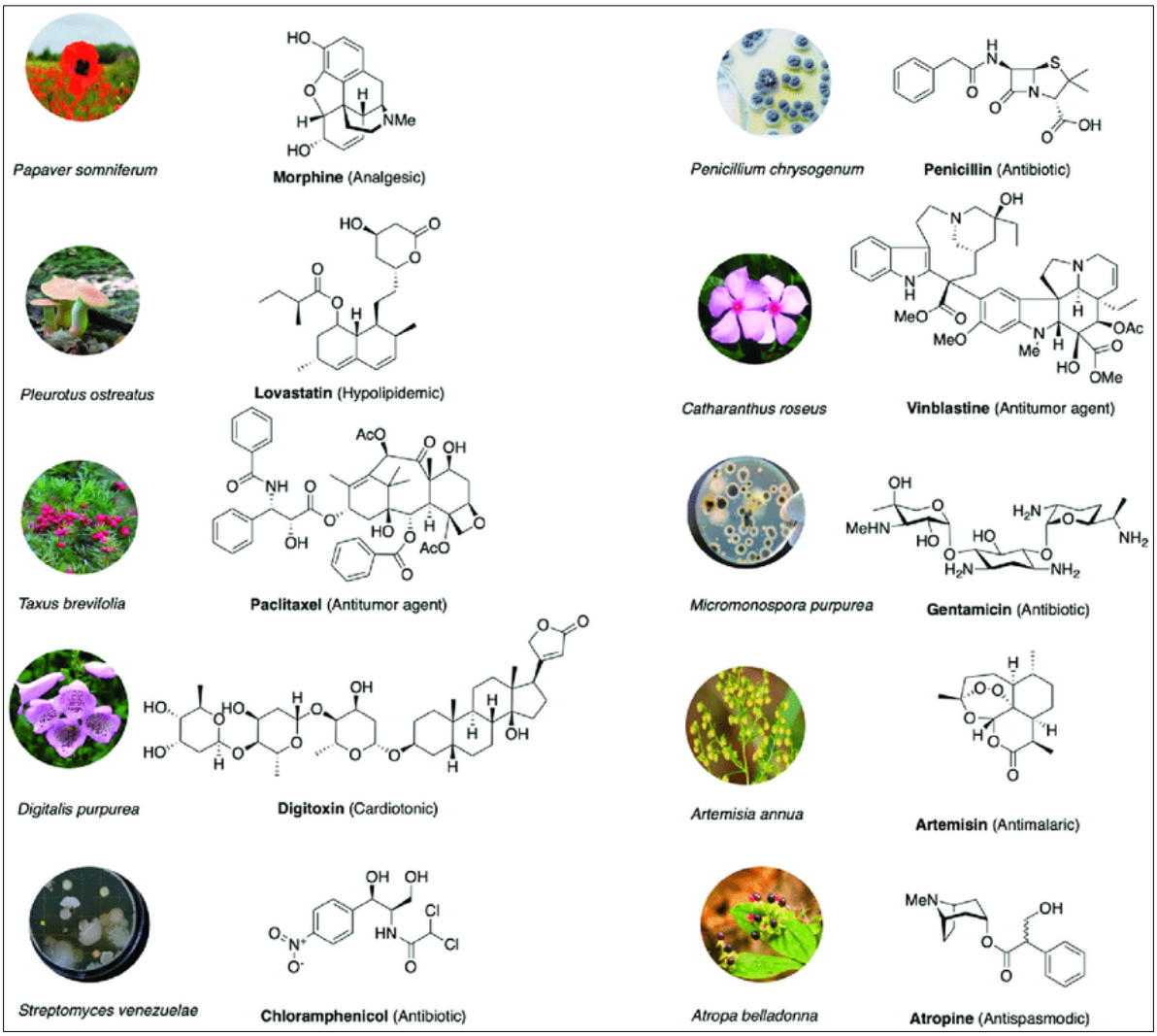

Figure 5 Nature as Source of Drugs

1.6. Jasmonates

Jasmonates are important in responses to injury and intracellular signals. They induce apoptosis and protein cascade via proteinase inhibitor, have defense functions, and regulate plant responses to different biotic and abiotic stresses. Jasmonates also have the ability to directly act on mitochondrial membranes by inducing membrane depolarization via release of metabolites.

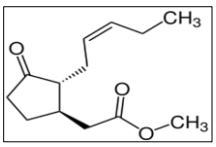

Figure 6 Chemical structure of methyl jasmonate (JA)

Jasmonate derivatives (JAD) are also important in wound response and tissue regeneration in plant cells. They have also been identified to have anti–aging effects on human epidermal layer. It is suspected that they interact with proteoglycans (PG) and glycosaminoglycan (GAG) polysaccharides, which are essential extracellular matrix (ECM) components to help remodel the ECM. The discovery of JADs on skin repair has introduced newfound interest in the effects of these plant hormones in therapeutic medicinal application.[7]

1.7. Salicylates

Salicylic acid (SA), a phytohormone, was initially derived from willow bark and has since been identified in many species. It is an important player in plant immunity, although its role is still not fully understood by scientists. They are involved in disease and immunity responses in plant and animal tissues. They have salicylic acid binding proteins (SABPs) that have shown to affect multiple animal tissues. The first discovered medicinal properties of the isolated compound was involved in pain and fever management. They also play an active role in the suppression of cell proliferation. They have the ability to induce death in lymphoblastic leukemia and other human cancer cells. One of the most common drugs derived from salicylates is aspirin, also known as acetylsalicylic acid, with anti–inflammatory and anti–pyretic properties.

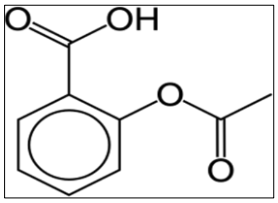

Figure 7 Chemical structure of acetylsalicylic acid, more commonly known as Aspirin

1.8. Microbial metabolites

Microbes compete for living space and nutrients. To survive in these conditions, many microbes have developed abilities to prevent competing species from proliferating. Microbes are the main source of antimicrobial drugs. Streptomyces isolates have been such a valuable source of antibiotics, that they have been called medicinal molds. The classic example of an antibiotic discovered as a defense mechanism against another microbe is penicillin in bacterial cultures contaminated by *Penicillium* fungi in 1928.

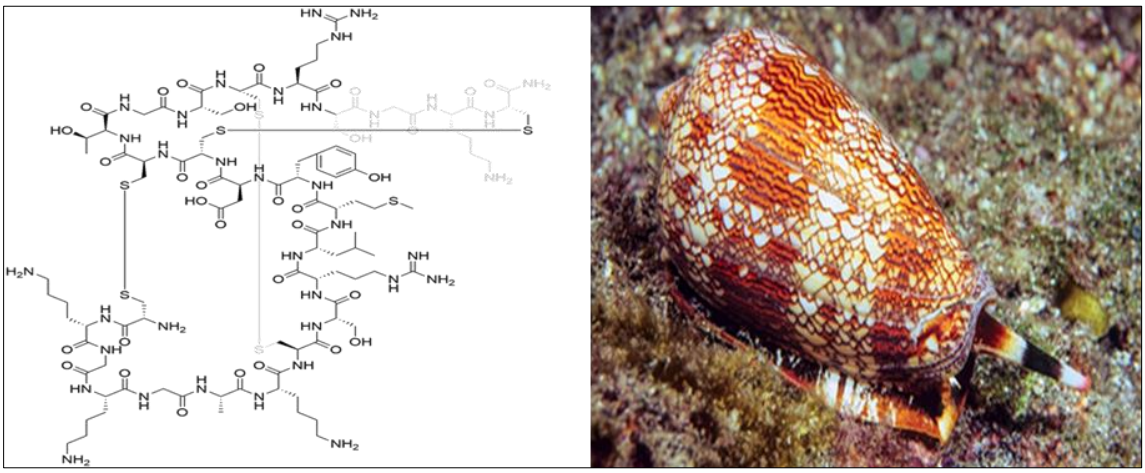

Figure 8 Ziconotide from cone snail

1.9. Marine invertebrates

Marine environments are potential sources for new bioactive agents. Arabinose nucleosides discovered from marine invertebrates in 1950s, demonstrated for the first time that sugar moieties other than ribose and deoxyribose can yield bioactive nucleoside structures. It took until 2004 when the first marine–derived drug was approved. For example, the cone snail toxin ziconotide, also known as Prialt treats severe neuropathic pain. Several other marine–derived agents are now in clinical trials for indications such as cancer, anti–inflammatory use and pain. One class of these agents are bryostatin–like compounds, under investigation as anti–cancer therapy.[8]

1.10. Chemical diversity

As above mentioned, combinatorial chemistry was a key technology enabling the efficient generation of large screening libraries for the needs of high–throughput screening. However, now, after two decades of combinatorial chemistry, it has been pointed out that despite the increased efficiency in chemical synthesis, no increase in lead or drug candidates

has been reached. This has led to analysis of chemical characteristics of combinatorial chemistry products, compared to existing drugs or natural products. The chemoinformatics concept chemical diversity, depicted as distribution of compounds in the chemical space based on their physicochemical characteristics, is often used to describe the difference between the combinatorial chemistry libraries and natural products. The synthetic, combinatorial library compounds seem to cover only a limited and quite uniform chemical space, whereas existing drugs and particularly natural products, exhibit much greater chemical diversity, distributing more evenly to the chemical space. The most prominent differences between natural products and compounds in combinatorial chemistry libraries is the number of chiral centers (much higher in natural compounds), structure rigidity (higher in natural compounds) and number of aromatic moieties (higher in combinatorial chemistry libraries). Other chemical differences between these two groups include the nature of heteroatoms (O and N enriched in natural products, and S and halogen atoms more often present in synthetic compounds), as well as level of non–aromatic unsaturation (higher in natural products). As both structure rigidity and chirality are well–established factors in medicinal chemistry known to enhance compounds specificity and efficacy as a drug, it has been suggested that natural products compare favourably to today's combinatorial chemistry libraries as potential lead molecules.

1.11. Screening

Two main approaches exist for the finding of new bioactive chemical entities from natural sources. The first is sometimes referred to as random collection and screening of material, but the collection is far from random. Biological (often botanical) knowledge is often used to identify families that show promise. This approach is effective because only a small part of the earth's biodiversity has ever been tested for pharmaceutical activity. Also, organisms living in a species–rich environment need to evolve defensive and competitive mechanisms to survive. Those mechanisms might be exploited in the development of beneficial drugs.

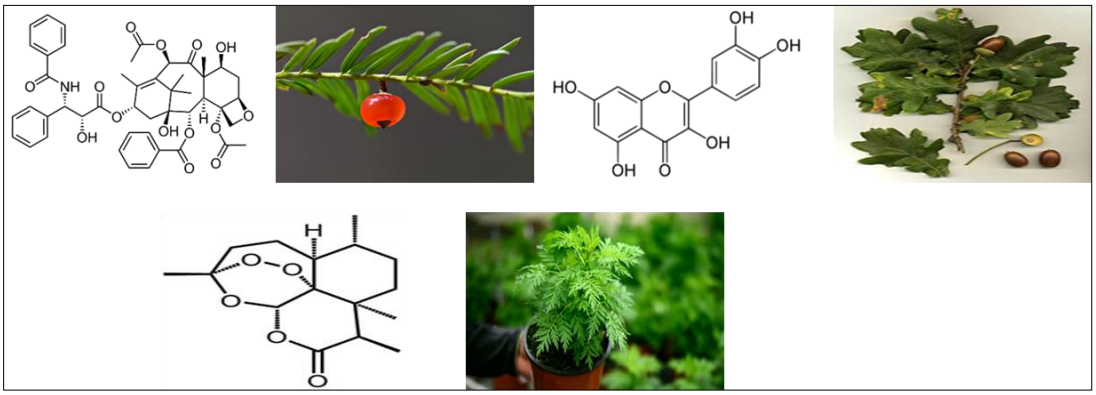

Figure 9 Paclitaxel from *Taxus brevifolia* and Quercetin from Oak and Artemisinin from *Artemisia annua*

A collection of plant, animal and microbial samples from rich ecosystems can potentially give rise to novel biological activities worth exploiting in the drug development process. One example of successful use of this strategy is the screening for antitumor agents by the National Cancer Institute, which started in the 1960s. Paclitaxel was identified from Pacific yew tree *Taxus brevifolia*. Paclitaxel showed anti–tumour activity by a previously undescribed mechanism (stabilization of microtubules) and is now approved for clinical use for the treatment of lung, breast, and ovarian cancer, as well as for Kaposi's sarcoma. Early in the 21st century, Cabazitaxel (made by Sanofi, a French firm), another relative of taxol has been shown effective against prostate cancer, also because it works by preventing the formation of microtubules, which pull the chromosomes apart in dividing cells (such as cancer cells). Other examples are:

- Camptotheca (Camptothecin · Topotecan · Irinotecan · Rubitecan · Belotecan);
- Podophyllum (Etoposide · Teniposide);
- Anthracyclines
  (Aclarubicin · Daunorubicin · Doxorubicin · Epirubicin · Idarubicin · Amrubicin · Pirarubicin · Valrubicin · Zor ubicin)
- Anthracenediones (Mitoxantrone · Pixantrone).

The second main approach involves ethnobotany, the study of the general use of plants in society, and ethnopharmacology, an area inside ethnobotany, which is focused specifically on medicinal uses. Artemisinin, an antimalarial agent from sweet wormtree *Artemisia annua*, used in Chinese medicine since 200BC is one drug used as part of combination therapy for multiresistant *Plasmodium falciparum*.

1.12. Structural elucidation

The elucidation of the chemical structure is critical to avoid the re–discovery of a chemical agent that is already known for its structure and chemical activity. Mass spectrometry is a method in which individual compounds are identified based on their mass/charge ratio, after ionization. Chemical compounds exist in nature as mixtures, so the combination of liquid chromatography and mass spectrometry (LC–MS) is often used to separate the individual chemicals. Databases of mass spectras for known compounds are available and can be used to assign a structure to an unknown mass spectrum. Nuclear magnetic resonance spectroscopy is the primary technique for determining chemical structures of natural products. NMR yields information about individual hydrogen and carbon atoms in the structure, allowing detailed reconstruction of the molecule's architecture.[9]

1.13. Clinical trials

are prospective biomedical or behavioral research studies on human participants designed to answer specific questions about biomedical or behavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. Clinical trials generate data on dosage, safety and efficacy. They are conducted only after they have received health authority/ethics committee approval in the country where approval of the therapy is sought. These authorities are responsible for vetting the risk/benefit ratio of the trial—their approval does not mean the therapy is 'safe' or effective, only that the trial may be conducted.

1.14. Overview: Trials of drugs

Some clinical trials involve healthy subjects with no pre–existing medical conditions. Other clinical trials pertain to people with specific health conditions who are willing to try an experimental treatment. Pilot experiments are conducted to gain insights for design of the clinical trial to follow. There are two goals to testing medical treatments: to learn whether they work well enough, called "efficacy" or "effectiveness"; and to learn whether they are safe enough, called "safety". Neither is an absolute criterion; both safety and efficacy are evaluated relative to how the treatment is intended to be used, what other treatments are available, and the severity of the disease or condition. The benefits must outweigh the risks. For example, many drugs to treat cancer have severe side effects that would not be acceptable for an over–the–counter pain medication, yet the cancer drugs have been approved since they are used under a physician's care and are used for a life–threatening condition. In the US, the elderly constitute 14% of the population, while they consume over one–third of drugs. People over 55 (or a similar cutoff age) are often excluded from trials because their greater health issues and drug use complicate data interpretation, and because they have different physiological capacity than younger people. Children and people with unrelated medical conditions are also frequently excluded. Pregnant women are often excluded due to potential risks to the foetus. The sponsor designs the trial in coordination with a panel of expert clinical investigators, including what alternative or existing treatments to compare to the new drug and what type(s) of patients might benefit. If the sponsor cannot obtain enough test subjects at one location investigators at other locations are recruited to join the study.

During the trial, investigators recruit subjects with the predetermined characteristics, administer the treatment(s) and collect data on the subjects' health for a defined time period. Data include measurements such as vital signs, concentration of the study drug in the blood or tissues, changes to symptoms, and whether improvement or worsening of the condition targeted by the study drug occurs. The researchers send the data to the trial sponsor, who then analyzes the pooled data using statistical tests.[10]

Examples of clinical trial goals include assessing the safety and relative effectiveness of a medication or device:

- On a specific kind of patient
- At varying dosages
- For a new indication
- Evaluation for improved efficacy in treating a condition as compared to the standard therapy for that condition
- Evaluation of the study drug or device relative to two or more already approved/common interventions for that condition.

While most clinical trials test one alternative to the novel intervention, some expand to three or four and may include a placebo. Except for small, single–location trials, the design and objectives are specified in a document called a clinical trial protocol. The protocol is the trial's "operating manual" and ensures all researchers perform the trial in the same way on similar subjects and that the data is comparable across all subjects. As a trial is designed to test hypotheses and rigorously monitor and assess outcomes, it can be seen as an application of the scientific method, specifically the

experimental step. The most common clinical trials evaluate new pharmaceutical products, medical devices, biologics, psychological therapies, or other interventions. Clinical trials may be required before a national regulatory authority approves marketing of the innovation.

1.15. Trials of devices

Similarly to drugs, manufacturers of medical devices in the United States are required to conduct clinical trials for premarket approval. Device trials may compare a new device to an established therapy, or may compare similar devices to each other. An example of the former in the field of vascular surgery is the Open versus Endovascular Repair (OVER trial) for the treatment of abdominal aortic aneurysm, which compared the older open aortic repair technique to the newer endovascular aneurysm repair device. An example of the latter are clinical trials on mechanical devices used in the management of adult female urinary incontinence.

1.16. Trials of procedures

Similarly to drugs, medical or surgical procedures may be subjected to clinical trials, such as case–controlled studies for surgical interventions.

1.17. Types

Clinical trials are classified by the research objective created by the investigators.

In an observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the study. In an *interventional study*, the investigators give the research subjects an experimental drug, surgical procedure, use of a medical device, diagnostic or other intervention to compare the treated subjects with those receiving no treatment or the standard treatment. Then the researchers assess how the subjects' health changes. Trials are classified by their purpose. After approval for human research is granted to the trial sponsor, the U.S. Food and Drug Administration (FDA) organizes and monitors the results of trials according to type:

- *Prevention* trials look for ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include drugs, vitamins or other micronutrients, vaccines, or lifestyle changes.
- *Screening* trials test for ways to identify certain diseases or health conditions.
- *Diagnostic* trials are conducted to find better tests or procedures for diagnosing a particular disease or condition.
- *Treatment* trials test experimental drugs, new combinations of drugs, or new approaches to surgery or radiation therapy.
- *Quality of life* trials (supportive care trials) evaluate how to improve comfort and quality of care for people with a chronic illness.
- *Genetic* trials are conducted to assess the prediction accuracy of genetic disorders making a person more or less likely to develop a disease.
- *Epidemiological* trials have the goal of identifying the general causes, patterns or control of diseases in large numbers of people.

Table 1 Phase trials in clinical aspect

Phase	Aim	Notes
Phase 0	Pharmacodynamics and pharma cokinetics in humans	Phase 0 trials are optional first–in–human trials. Single subtherapeutic doses of the study drug or treatment are given to a small number of subjects (typically 10 to 15) to gather preliminary data on the agent's pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drugs). For a test drug, the trial documents the absorption, distribution, metabolization, and clearance (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected.

Phase I	Screening for safety	Often are first–in–person trials. Testing within a small group of people (typically 20–80) to evaluate safety, determine safe dosage ranges, and identify side effects.
Phase II	Establishing the preliminary efficacy of the drug in a "treatment group", usually against a placebo control group	Phase IIa is specifically designed to assess dosing requirements (how much drug should be given), while a Phase IIb trial is designed to determine efficacy, and studies how well the drug works at the prescribed dose(s), establishing a therapeutic dose range.
Phase III	Final confirmation of safety and efficacy	Testing with large groups of people (typically 1,000–3,000) to confirm its efficacy, evaluate its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.
Phase IV	Safety studies during sales	Postmarketing studies delineate risks, benefits, and optimal use. As such, they are ongoing during the drug's lifetime of active medical use.

- *Compassionate use* trials or expanded access trials provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy has been approved, or a patient who has already failed all standard treatments and whose health is too compromised to qualify for participation in randomized clinical trials. Usually, case–by–case approval must be granted by both the FDA and the pharmaceutical company for such exceptions.
- Fixed trials consider existing data only during the trial's design, do not modify the trial after it begins, and do not assess the results until the study is completed.
- Adaptive clinical trials use existing data to design the trial, and then use interim results to modify the trial as it proceeds. Modifications include dosage, sample size, drug undergoing trial, patient selection criteria and "cocktail" mix. Adaptive trials often employ a Bayesian experimental design to assess the trial's progress. In some cases, trials have become an ongoing process that regularly adds and drops therapies and patient groups as more information is gained. The aim is to more quickly identify drugs that have a therapeutic effect and to zero in on patient populations for whom the drug is appropriate. Clinical trials are conducted typically in four phases, with each phase using different numbers of subjects and having a different purpose to construct focus on identifying a specific effect.

1.18. Phases

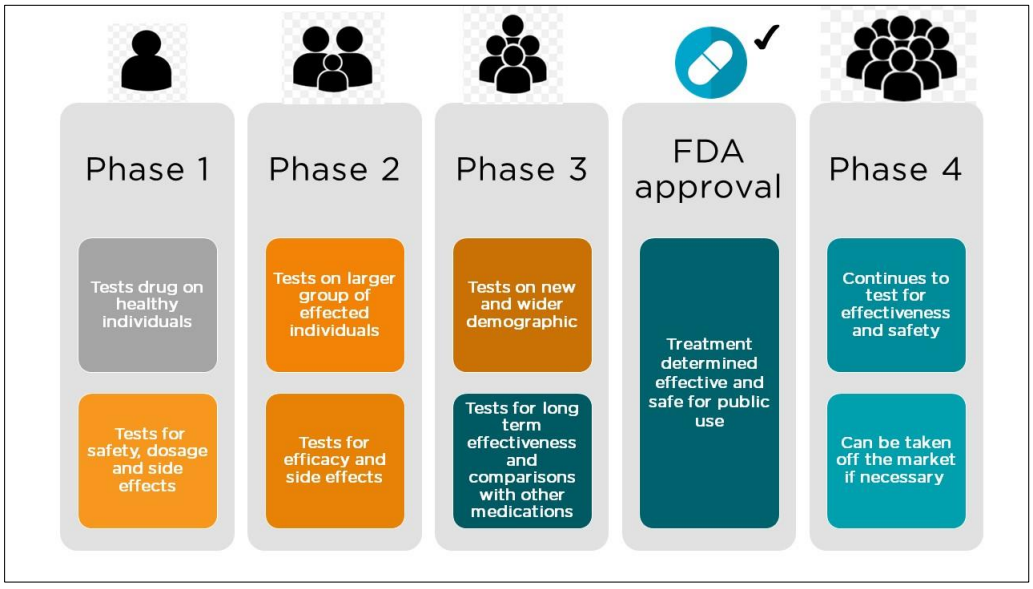

Figure 10 Different phases of Clinical Trials

Clinical trials involving new drugs are commonly classified into five phases. Each phase of the drug approval process is treated as a separate clinical trial. The drug development process will normally proceed through phase's I–IV over many years, frequently involving a decade or longer. If the drug successfully passes through phases I, II, and III, it will usually be approved by the national regulatory authority for use in the general population. Phase IV trials are performed after the newly approved drug, diagnostic or device is marketed, providing assessment about risks, benefits, or best uses.

1.19. Trial design

A fundamental distinction in evidence–based practice is between observational studies and randomized controlled trials. Types of observational studies in epidemiology, such as the cohort study and the case–control study, provide less compelling evidence than the randomized controlled trial. In observational studies, the investigators retrospectively assess associations between the treatments given to participants and their health status, with potential for considerable errors in design and interpretation. A randomized controlled trial can provide compelling evidence that the study treatment causes an effect on human health. Currently, some Phase II and most Phase III drug trials are designed as randomized, double–blind, and placebo–controlled.

1.20. Randomized

Each study subject is randomly assigned to receive either the study treatment or a placebo.

1.20.1. Blind

The subjects involved in the study do not know which study treatment they receive. If the study is double–blind, the researchers also do not know which treatment a subject receives. This intent is to prevent researchers from treating the two groups differently. A form of double–blind study called a "double–dummy" design allows additional insurance against bias. In this kind of study, all patients are given both placebo and active doses in alternating periods.

1.20.2. Placebo–controlled

The use of a placebo (fake treatment) allows the researchers to isolate the effect of the study treatment from the placebo effect.

Clinical studies having small numbers of subjects may be "sponsored" by single researchers or a small group of researchers, and are designed to test simple questions or feasibility to expand the research for a more comprehensive randomized controlled trial.

1.20.3. Active control studies

In many cases, giving a placebo to a person suffering from a disease may be unethical. To address this, it has become a common practice to conduct "active comparator" (also known as "active control") trials. In trials with an active control group, subjects are given either the experimental treatment or a previously approved treatment with known effectiveness.

1.20.4. Master protocol

In such studies, multiple experimental treatments are tested in a single trial. Genetic testing enables researchers to group patients according to their genetic profile, deliver drugs based on that profile to that group and compare the results. Multiple companies can participate, each bringing a different drug. The first such approach targets squamous cell cancer, which includes varying genetic disruptions from patient to patient. Amgen, AstraZeneca and Pfizer are involved, the first time they have worked together in a late–stage trial. Patients whose genomic profiles do not match any of the trial drugs receive a drug designed to stimulate the immune system to attack cancer.

1.20.5. Clinical trial protocol

A clinical trial protocol is a document used to define and manage the trial. It is prepared by a panel of experts. All study investigators are expected to strictly observe the protocol. The protocol describes the scientific rationale, objective(s), design, methodology, statistical considerations and organization of the planned trial. Details of the trial are provided in documents referenced in the protocol, such as an investigator's brochure. The protocol contains a precise study plan to assure safety and health of the trial subjects and to provide an exact template for trial conduct by investigators. This allows data to be combined across all investigators/sites. The protocol also informs the study administrators (often a contract research organization).

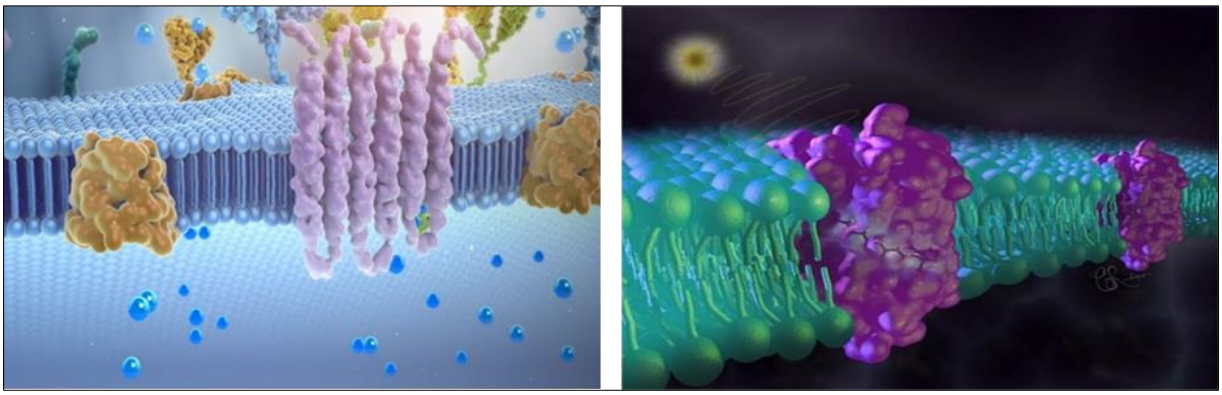

Figure 11 Drug-Receptor binding

The format and content of clinical trial protocols sponsored by pharmaceutical, biotechnology or medical device companies in the United States, European Union, or Japan have been standardized to follow Good Clinical Practice guidance issued by the International Conference on Harmonization [ICH] of Technical Requirements for Registration of Pharmaceuticals for Human Use. Regulatory authorities in Canada and Australia also follow ICH guidelines. Journals such as *Trials*, encourage investigators to publish their protocols.

Subject Information and Consent Form

A Phase 3, Double-Blind, Placebo-Controlled Study of Maintenance Pemetrexed plus Best Supportive Care versus Best Supportive Care Immediately Following Induction Treatment with Pemetrexed + Cisplatin for Advanced Non-Squamous Non-Small Cell Lung Cancer

Qualified Investigator: [Insert name and contact information]
Sub-Investigator(s): [Insert name(s) and contact information, if required]
Sponsor: **Eli Lilly Canada Inc.**

Introduction

You are being invited to take part in a research study *(also called a clinical trial)*. This research will study a drug known as pemetrexed (Alimta®). It is your choice if you want to be in this study or not. Research studies are different from regular care. Research studies are ways of finding out new information that might help other people with similar conditions or illnesses to yours. This form explains why we are doing the study, and how the treatment that is being offered to you is different from regular care. It tells you what will happen during the study. It also tells you about any inconvenience, discomfort or risk with this study. It also gives you a complete description of the treatment offered. This information will help you decide whether you wish to be part of the study.

What Is The Purpose of The Study?

The main reason for doing this study is to help answer the following research question:

- Whether the administration of pemetrexed as a maintenance treatment will improve upon therapy you initially received (pemetrexed in combination with cisplatin) and will prevent your cancer from growing or recurring.

Who Can Take Part In The Study?

To take part in this study you must have the diagnosis of unresectable, locally advanced, stage IIIB or stage IV, non-squamous non-small cell lung cancer. The study doctor or study staff has discussed with you the requirements for being in this study. It is important that you are completely honest with the doctor and staff about your health history. You should not take part in this study if you do not meet all requirements.

You cannot participate in this study if:

- You have an active infection or other serious condition such as cardiac disease
- You have had another malignant cancer less than five years ago
- You take aspirin or aspirin like medication that you are unable to stop taking for a few days during each cycle of therapy
- You are unable or unwilling to take folic acid, vitamin B12 and dexamethasone or other corticosteroids medication.
- You have had a yellow fever vaccination within the last 30 days or plan to have it.

Figure 12 Example of informed consent document from the PARAMOUNT trial

1.21. Design features: Informed consent

Clinical trials recruit study subjects to sign a document representing their "informed consent". The document includes details such as its purpose, duration, required procedures, risks, potential benefits, key contacts and institutional requirements. The participant then decides whether to sign the document. The document is not a contract, as the participant can withdraw at any time without penalty. Informed consent is a legal process in which a recruit is instructed about key facts before deciding whether to participate. Researchers explain the details of the study in terms the subject can understand. The information is presented in the subject's native language. Generally, children cannot autonomously provide informed consent, but depending on their age and other factors, may be required to provide informed assent.

1.22. Statistical power

In any clinical trial, the number of subjects, also called the sample size, has a large impact on the ability to reliably detect and measure the effects of the intervention. This ability is described as its "power", which must be calculated before initiating a study to figure out if the study is worth its costs. In general, a larger sample size increases the statistical power, also the cost. The statistical power estimates the ability of a trial to detect a difference of a particular size (or larger) between the treatment and control groups. For example, a trial of a lipid–lowering drug versus placebo with 100 patients in each group might have a power of 0.90 to detect a difference between placebo and trial groups receiving dosage of 10 mg/dL or more, but only 0.70 to detect a difference of 6 mg/dL.[11]

1.23. Placebo groups

Merely giving a treatment can have nonspecific effects. These are controlled for by the inclusion of patients who receive only a placebo. Subjects are assigned randomly without informing them to which group they belonged. Many trials are double–blinded so that researchers do not know to which group a subject is assigned. Assigning a subject to a placebo group can pose an ethical problem if it violates his or her right to receive the best available treatment. The Declaration of Helsinki provides guidelines on this issue.

1.24. Duration

Clinical trials are only a small part of the research that goes into developing a new treatment. Potential drugs, for example, first have to be discovered, purified, characterized, and tested in labs (in cell and animal studies) before ever undergoing clinical trials. In all, about 1,000 potential drugs are tested before just one reaches the point of being tested in a clinical trial. For example, a new cancer drug has, on average, six years of research behind it before it even makes it to clinical trials.

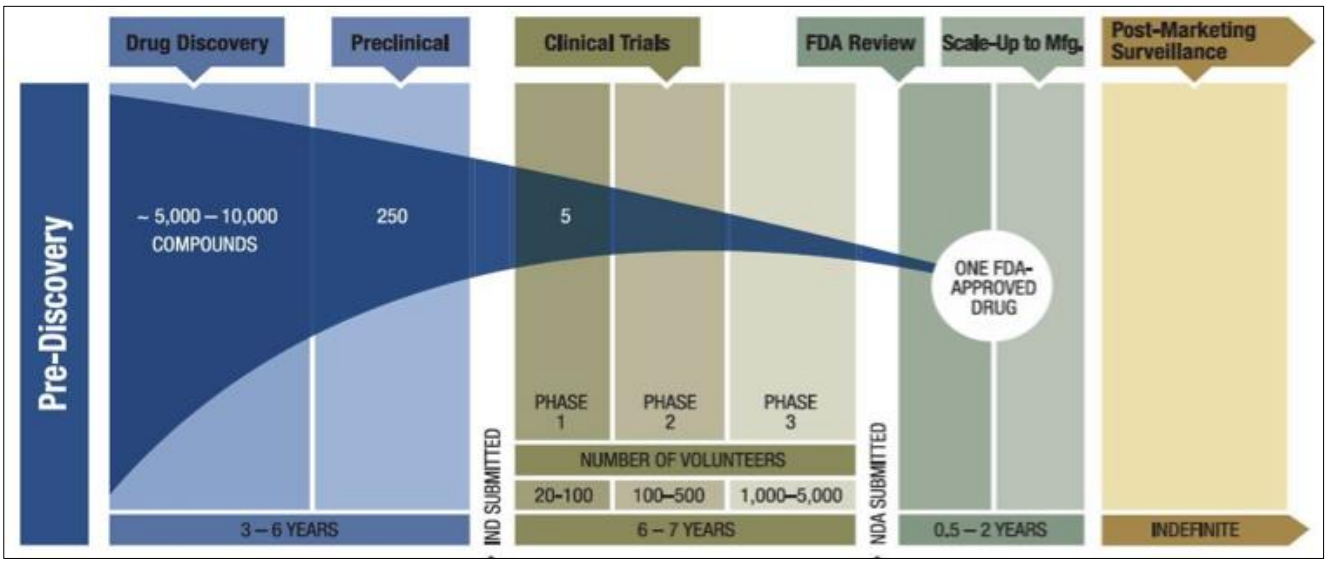

Figure 13 Timeline of various approval tracks and research phases in the US

But the major holdup in making new cancer drugs available is the time it takes to complete clinical trials themselves. On average, about eight years pass from the time a cancer drug enters clinical trials until it receives approval from regulatory agencies for sale to the public. Drugs for other diseases have similar timelines.

Some reasons a clinical trial might last several years:

- For chronic conditions such as cancer, it takes months, if not years, to see if a cancer treatment has an effect on a patient.
- For drugs that are not expected to have a strong effect (meaning a large number of patients must be recruited to observe 'any' effect), recruiting enough patients to test the drug's effectiveness (i.e., getting statistical power) can take several years.
- Only certain people who have the target disease condition are eligible to take part in each clinical trial. Researchers who treat these particular patients must participate in the trial. Then they must identify the desirable patients and obtain consent from them or their families to take part in the trial.

A clinical trial might also include an extended post–study follow–up period from months to years for people who have participated in the trial, a so–called "extension phase", which aims to identify long–term impact of the treatment. The biggest barrier to completing studies is the shortage of people who take part. All drug and many device trials target a subset of the population, meaning not everyone can participate. Some drug trials require patients to have unusual combinations of disease characteristics. It is a challenge to find the appropriate patients and obtain their consent, especially when they may receive no direct benefit (because they are not paid, the study drug is not yet proven to work, or the patient may receive a placebo). In the case of cancer patients, fewer than 5% of adults with cancer will participate in drug trials. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), about 400 cancer medicines were being tested in clinical trials in 2005. Not all of these will prove to be useful, but those that are may be delayed in getting approved because the number of participants is so low. For clinical trials involving potential for seasonal influences (such as airborne allergies, seasonal affective disorder, influenza, and skin diseases), the study may be done during a limited part of the year (such as spring for pollen allergies), when the drug can be tested.

Clinical trials that do not involve a new drug usually have a much shorter duration. (Exceptions are epidemiological studies, such as the Nurses' Health Study).

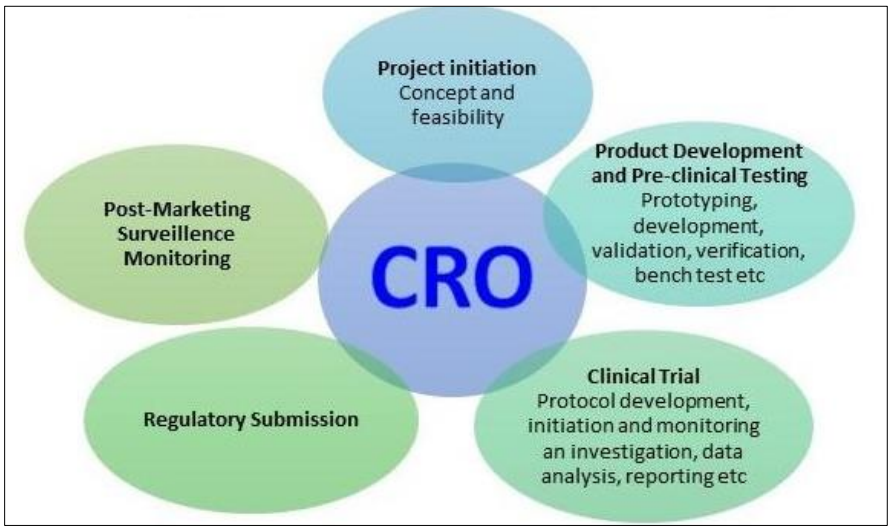

Figure 14 CRO

1.25. Administration

Clinical trials designed by a local investigator, and (in the US) federally funded clinical trials, are almost always administered by the researcher who designed the study and applied for the grant. Small–scale device studies may be administered by the sponsoring company. Clinical trials of new drugs are usually administered by a contract research organization (CRO) hired by the sponsoring company. The sponsor provides the drug and medical oversight. A CRO is contracted to perform all the administrative work on a clinical trial. For Phases II–IV the CRO recruits participating researchers, trains them, provides them with supplies, coordinates study administration and data collection, sets up meetings, monitors the sites for compliance with the clinical protocol, and ensures the sponsor receives data from every site. Specialist site management organizations can also be hired to coordinate with the CRO to ensure rapid IRB/IEC approval and faster site initiation and patient recruitment. Phase I clinical trials of new medicines are often conducted in a specialist clinical trial clinic, with dedicated pharmacologists, where the subjects can be observed by full–time staff.

These clinics are often run by a CRO which specialises in these studies. At a participating site, one or more research assistants (often nurses) do most of the work in conducting the clinical trial. The research assistant's job can include some or all of the following: providing the local institutional review board (IRB) with the documentation necessary to obtain its permission to conduct the study, assisting with study start–up, identifying eligible patients, obtaining consent from them or their families, administering study treatment(s), collecting and statistically analyzing data, maintaining and updating data files during follow–up, and communicating with the IRB, as well as the sponsor and CRO.[12]

1.26. Quality

In the context of a clinical trial, quality typically refers to the absence of errors which can impact decision making, both during the conduct of the trial and in use of the trial results.

1.27. Marketing

Janet Yang uses the Interactional Justice Model to test the effects of willingness to talk with a doctor and clinical trial enrollment. Results found that potential clinical trial candidates were less likely to enroll in clinical trials if the patient is more willing to talk with their doctor. The reasoning behind this discovery may be patients are happy with their current care. Another reason for the negative relationship between perceived fairness and clinical trial enrollment is the lack of independence from the care provider. Results found that there is a positive relationship between a lack of willingness to talk with their doctor and clinical trial enrollment. Lack of willingness to talk about clinical trials with current care providers may be due to patients' independence from the doctor. Patients who are less likely to talk about clinical trials are more willing to use other sources of information to gain a better insight of alternative treatments. Clinical trial enrollment should be motivated to utilize websites and television advertising to inform the public about clinical trial enrolment.

1.28. Information technology

The last decade has seen a proliferation of information technology use in the planning and conduct of clinical trials. Clinical trial management systems are often used by research sponsors or CROs to help plan and manage the operational aspects of a clinical trial, particularly with respect to investigational sites. Advanced analytics for identifying researchers and research sites with expertise in a given area utilize public and private information about ongoing research. Web–based electronic data capture (EDC) and clinical data management systems are used in a majority of clinical trials to collect case report data from sites, manage its quality and prepare it for analysis. Interactive voice response systems are used by sites to register the enrollment of patients using a phone and to allocate patients to a particular treatment arm (although phones are being increasingly replaced with web–based (IWRS) tools which are sometimes part of the EDC system). While patient–reported outcome were often paper based in the past, measurements are increasingly being collected using web portals or hand–held ePRO (or eDiary) devices, sometimes wireless. Statistical software is used to analyze the collected data and prepare them for regulatory submission. Access to many of these applications are increasingly aggregated in web–based clinical trial portals. In 2011, the FDA approved a Phase I trial that used telemonitoring, also known as remote patient monitoring, to collect biometric data in patients' homes and transmit it electronically to the trial database. This technology provides many more data points and is far more convenient for patients, because they have fewer visits to trial sites.[13]

1.29. Ethical aspects

Clinical trials are closely supervised by appropriate regulatory authorities. All studies involving a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial. The local ethics committee has discretion on how it will supervise no interventional studies (observational studies or those using already collected data). In the US, this body is called the Institutional Review Board (IRB); in the EU, they are called Ethics committees. Most IRBs are located at the local investigator's hospital or institution, but some sponsors allow the use of a central (independent/for profit) IRB for investigators who work at smaller institutions.[14]

To be ethical, researchers must obtain the full and informed consent of participating human subjects. (One of the IRB's main functions is to ensure potential patients are adequately informed about the clinical trial.) If the patient is unable to consent for him/herself, researchers can seek consent from the patient's legally authorized representative. In California, the state has prioritized the individuals who can serve as the legally authorized representative. In some US locations, the local IRB must certify researchers and their staff before they can conduct clinical trials. They must understand the federal patient privacy (HIPAA) law and good clinical practice. The International Conference of Harmonisation Guidelines for Good Clinical Practice is a set of standards used internationally for the conduct of clinical trials. The guidelines aim to ensure the "rights, safety and well–being of trial subjects are protected".

The notion of informed consent of participating human subjects exists in many countries but its precise definition may still vary. Informed consent is clearly a 'necessary' condition for ethical conduct but does not 'ensure' ethical conduct. In compassionate use trials the latter becomes a particularly difficult problem. The final objective is to serve the community of patients or future patients in a best–possible and most responsible way. See also Expanded access. However, it may be hard to turn this objective into a well–defined, quantified, objective function. In some cases this can be done, however, for instance, for questions of when to stop sequential treatments, and then quantified methods may play an important role. Additional ethical concerns are present when conducting clinical trials on children (pediatrics), and in emergency or epidemic situations. Ethically balancing the rights of multiple stakeholders may be difficult. For example, when drug trials fail, the sponsors may have a duty to tell current and potential investors immediately, which means both the research staff and the enrolled participants may first hear about the end of a trial through public business news.[15]

1.30. Conflicts of interest and unfavourable studies

In response to specific cases in which unfavorable data from pharmaceutical company–sponsored research were not published, the Pharmaceutical Research and Manufacturers of America published new guidelines urging companies to report all findings and limit the financial involvement in drug companies by researchers. The US Congress signed into law a bill which requires Phase II and Phase III clinical trials to be registered by the sponsor on the clinicaltrials.gov website compiled by the National Institutes of Health. Drug researchers not directly employed by pharmaceutical companies often seek grants from manufacturers, and manufacturers often look to academic researchers to conduct studies within networks of universities and their hospitals, e.g., for translational cancer research. Similarly, competition for tenured academic positions, government grants and prestige create conflicts of interest among academic scientists. According to one study, approximately 75% of articles retracted for misconduct–related reasons have no declared industry financial support. Seeding trials are particularly controversial. In the United States, all clinical trials submitted to the FDA as part of a drug approval process are independently assessed by clinical experts within the Food and Drug Administration, including inspections of primary data collection at selected clinical trial sites. In 2001, the editors of 12 major journals issued a joint editorial, published in each journal, on the control over clinical trials exerted by sponsors, particularly targeting the use of contracts which allow sponsors to review the studies prior to publication and withhold publication. They strengthened editorial restrictions to counter the effect. The editorial noted that contract research organizations had, by 2000, received 60% of the grants from pharmaceutical companies in the US. Researchers may be restricted from contributing to the trial design, accessing the raw data, and interpreting the results.[16]

Despite explicit recommendations by stakeholders of measures to improve the standards of industry–sponsored medical research, in 2013, Tohen warned of the persistence of a gap in the credibility of conclusions arising from industry–funded clinical trials, and called for ensuring strict adherence to ethical standards in industrial collaborations with academia, in order to avoid further erosion of the public's trust. Issues referred for attention in this respect include potential observation bias, duration of the observation time for maintenance studies, the selection of the patient populations, factors that affect placebo response, and funding sources.[17]

1.31. During public health crises

Conducting clinical trials of vaccines during epidemics and pandemics is subject to ethical concerns. For diseases with high mortality rates like Ebola, assigning individuals to a placebo or control group can be viewed as a death sentence. In response to ethical concerns regarding clinical research during epidemics, the National Academy of Medicine authored a report identifying seven ethical and scientific considerations. These considerations are:

- Scientific value
- Social value
- Respect for persons
- Community engagement
- Concern for participant welfare and interests
- A balance towards benefit over risks
- Post–trial access to tested therapies that had been withheld during the trial

1.32. Pregnant women and children

Pregnant women and children are typically excluded from clinical trials as vulnerable populations, though the data to support excluding them is not robust. By excluding them from clinical trials, information about the safety and effectiveness of therapies for these populations is often lacking. During the early history of the HIV/AIDS epidemic, a

scientist noted that by excluding these groups from potentially life–saving treatment, they were being "protected to death". Projects such as Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) have advocated for the ethical inclusion of pregnant women in vaccine trials. Inclusion of children in clinical trials has additional moral considerations, as children lack decision–making autonomy. Trials in the past had been criticized for using hospitalized children or orphans; these ethical concerns effectively stopped future research. In efforts to maintain effective pediatric care, several European countries and the US have policies to entice or compel pharmaceutical companies to conduct pediatric trials. International guidance recommends ethical pediatric trials by limiting harm, considering varied risks, and taking into account the complexities of paediatric care.[18]

1.33. Safety

Responsibility for the safety of the subjects in a clinical trial is shared between the sponsor, the local site investigators (if different from the sponsor), the various IRBs that supervise the study, and (in some cases, if the study involves a marketable drug or device), the regulatory agency for the country where the drug or device will be sold. A systematic concurrent safety review is frequently employed to assure research participant safety. The conduct and on–going review is designed to be proportional to the risk of the trial. Typically this role is filled by a Data and Safety Committee, an externally appointed Medical Safety Monitor, an Independent Safety Officer, or for small or low–risk studies the principal investigator.

For safety reasons, many clinical trials of drugs are designed to exclude women of childbearing age, pregnant women, or women who become pregnant during the study. In some cases, the male partners of these women are also excluded or required to take birth control measures.[19]

1.34. Sponsor

Throughout the clinical trial, the sponsor is responsible for accurately informing the local site investigators of the true historical safety record of the drug, device or other medical treatments to be tested, and of any potential interactions of the study treatment(s) with already approved treatments. This allows the local investigators to make an informed judgment on whether to participate in the study or not. The sponsor is also responsible for monitoring the results of the study as they come in from the various sites as the trial proceeds. In larger clinical trials, a sponsor will use the services of a data monitoring committee (DMC, known in the US as a data safety monitoring board). This independent group of clinicians and statisticians meets periodically to review the unblinded data the sponsor has received so far. The DMC has the power to recommend termination of the study based on their review, for example if the study treatment is causing more deaths than the standard treatment, or seems to be causing unexpected and study–related serious adverse events. The sponsor is responsible for collecting adverse event reports from all site investigators in the study, and for informing all the investigators of the sponsor's judgment as to whether these adverse events were related or not related to the study treatment. The sponsor and the local site investigators are jointly responsible for writing a site–specific informed consent that accurately informs the potential subjects of the true risks and potential benefits of participating in the study, while at the same time presenting the material as briefly as possible and in ordinary language. FDA regulations state that participating in clinical trials is voluntary, with the subject having the right not to participate or to end participation at any time.[20]

1.35. Local site investigators

The ethical principle of *primum non–nocere* ("first, do no harm") guides the trial, and if an investigator believes the study treatment may be harming subjects in the study, the investigator can stop participating at any time. On the other hand, investigators often have a financial interest in recruiting subjects, and could act unethically to obtain and maintain their participation. The local investigators are responsible for conducting the study according to the study protocol, and supervising the study staff throughout the duration of the study. The local investigator or his/her study staff are also responsible for ensuring the potential subjects in the study understand the risks and potential benefits of participating in the study. In other words, they (or their legally authorized representatives) must give truly informed consent.[21]

Local investigators are responsible for reviewing all adverse event reports sent by the sponsor. These adverse event reports contain the opinions of both the investigator (at the site where the adverse event occurred) and the sponsor, regarding the relationship of the adverse event to the study treatments. Local investigators also are responsible for making an independent judgment of these reports, and promptly informing the local IRB of all serious and study treatment–related adverse events. When a local investigator is the sponsor, there may not be formal adverse event reports, but study staff at all locations are responsible for informing the coordinating investigator of anything unexpected. The local investigator is responsible for being truthful to the local IRB in all communications relating to the study.[22]

1.36. Institutional review boards (IRBs)

Approval by an Institutional Review Board (IRB), or Independent Ethics Committee (IEC), is necessary before all but the most informal research can begin. In commercial clinical trials, the study protocol is not approved by an IRB before the sponsor recruits sites to conduct the trial. However, the study protocol and procedures have been tailored to fit generic IRB submission requirements. In this case, and where there is no independent sponsor, each local site investigator submits the study protocol, the consent(s), the data collection forms, and supporting documentation to the local IRB. Universities and most hospitals have in–house IRBs. Other researchers (such as in walk–in clinics) use independent IRBs. The IRB scrutinizes the study both for medical safety and for protection of the patients involved in the study, before it allows the researcher to begin the study. It may require changes in study procedures or in the explanations given to the patient. A required yearly "continuing review" report from the investigator updates the IRB on the progress of the study and any new safety information related to the study.[23]

1.37. Regulatory agencies

In the US, the FDA can audit the files of local site investigators after they have finished participating in a study, to see if they were correctly following study procedures. This audit may be random, or for cause (because the investigator is suspected of fraudulent data). Avoiding an audit is an incentive for investigators to follow study procedures. A 'covered clinical study' refers to a trial submitted to the FDA as part of a marketing application (for example, as part of an NDA or 510(k)), about which the FDA may require disclosure of financial interest of the clinical investigator in the outcome of the study. For example, the applicant must disclose whether an investigator owns equity in the sponsor, or owns proprietary interest in the product under investigation. The FDA defines a covered study as "... any study of a drug, biological product or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety."[24]

Alternatively, many American pharmaceutical companies have moved some clinical trials overseas. Benefits of conducting trials abroad include lower costs (in some countries) and the ability to run larger trials in shorter timeframes, whereas a potential disadvantage exists in lower–quality trial management. Different countries have different regulatory requirements and enforcement abilities. An estimated 40% of all clinical trials now take place in Asia, Eastern Europe, and Central and South America. "There is no compulsory registration system for clinical trials in these countries and many do not follow European directives in their operations", says Jacob Sijtsma of the Netherlands–based WEMOS, an advocacy health organisation tracking clinical trials in developing countries.[25]

Beginning in the 1980s, harmonization of clinical trial protocols was shown as feasible across countries of the European Union. At the same time, coordination between Europe, Japan and the United States led to a joint regulatory–industry initiative on international harmonization named after 1990 as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Currently, most clinical trial programs follow ICH guidelines, aimed at "ensuring that good quality, safe and effective medicines are developed and registered in the most efficient and cost–effective manner. These activities are pursued in the interest of the consumer and public health, to prevent unnecessary duplication of clinical trials in humans and to minimize the use of animal testing without compromising the regulatory obligations of safety and effectiveness."[26]

1.38. Aggregation of safety data during clinical development

Aggregating safety data across clinical trials during drug development is important because trials are generally designed to focus on determining how well the drug works. The safety data collected and aggregated across multiple trials as the drug is developed allows the sponsor, investigators and regulatory agencies to monitor the aggregate safety profile of experimental medicines as they're developed. The value of assessing aggregate safety data is: a) decisions based on aggregate safety assessment during development of the medicine can be made throughout the medicine's development and b) it sets up the sponsor and regulators well for assessing the medicine's safety after the drug is approved.[27]

1.39. Economics

Clinical trial costs vary depending on trial phase, type of trial, and disease studied. A study of clinical trials conducted in the United States from 2004 to 2012 found the average cost of Phase I trials to be between $1.4 million and $6.6 million, depending on the type of disease. Phase II trials ranged from $7 million to $20 million, and Phase III trials from $11 million to $53 million.[28]

1.40. Sponsor

The cost of a study depends on many factors, especially the number of sites conducting the study, the number of patients involved, and whether the study treatment is already approved for medical use. The expenses incurred by a pharmaceutical company in administering a Phase III or IV clinical trial may include, among others:

- Production of the drug(s) or device(s) being evaluated.
- Staff salaries for the designers and administrators of the trial.
- Payments to the contract research organization, the site management organization (if used) and any outside consultants
- Payments to local researchers and their staff for their time and effort in recruiting test subjects and collecting data for the sponsor.
- The cost of study materials and the charges incurred to ship them.
- Communication with the local researchers, including on–site monitoring by the CRO before and (in some cases) multiple times during the study.
- One or more investigator training meetings.
- Expense incurred by the local researchers, such as pharmacy fees, IRB fees and postage.
- Any payments to subjects enrolled in the trial.
- The expense of treating a test subject who develops a medical condition caused by the study drug.

These expenses are incurred over several years. In the US, sponsors may receive a 50 percent tax credit for clinical trials conducted on drugs being developed for the treatment of orphan diseases. National health agencies, such as the US National Institutes of Health, offer grants to investigators who design clinical trials that attempt to answer research questions of interest to the agency. In these cases, the investigator who writes the grant and administers the study acts as the sponsor, and coordinates data collection from any other sites. These other sites may or may not be paid for participating in the study, depending on the amount of the grant and the amount of effort expected from them. Using internet resources can, in some cases, reduce the economic burden.[29]

1.41. Investigators

Investigators are often compensated for their work in clinical trials. These amounts can be small, just covering a partial salary for research assistants and the cost of any supplies (usually the case with national health agency studies), or be substantial and include "overhead" that allows the investigator to pay the research staff during times between clinical trials.[30]

1.41.1. Subjects

Participants in Phase I drug trials do not gain any direct health benefit from taking part. They are generally paid a fee for their time, with payments regulated and not related to any risk involved. Motivations of healthy volunteers is not limited to financial reward and may include other motivations such as contributing to science and others. In later phase trials, subjects may not be paid to ensure their motivation for participating with potential for a health benefit or contributing to medical knowledge. Small payments may be made for study–related expenses such as travel or as compensation for their time in providing follow–up information about their health after the trial treatment ends.[31]

1.42. Participant recruitment and participation

Phase 0 and Phase I drug trials seek healthy volunteers. Most other clinical trials seek patients who have a specific disease or medical condition. The diversity observed in society should be reflected in clinical trials through the appropriate inclusion of ethnic minority populations. Patient recruitment or participant recruitment plays a significant role in the activities and responsibilities of sites conducting clinical trials. All volunteers being considered for a trial are required to undertake a medical screening. Requirements differ according to the trial needs, but typically volunteers would be screened in a medical laboratory for:

- Measurement of the electrical activity of the heart (ECG)
- Measurement of blood pressure, heart rate, and body temperature
- Blood sampling
- Urine sampling
- Weight and height measurement
- Drug abuse testing
- Pregnancy testing

Figure 15 Newspaper advertisements seeking patients and healthy volunteers to participate in clinical trials

It has been observed that participants in clinical trials are disproportionately white. One recent systematic review of the literature found that race/ethnicity as well as sex were not well–represented nor at times even tracked as participants in a large number of clinical trials of hearing loss management in adults. This may reduce the validity of findings in respect of non–white patients by not adequately representing the larger population.[32]

1.43. Locating trials

Depending on the kind of participants required, sponsors of clinical trials, or contract research organizations working on their behalf, try to find sites with qualified personnel as well as access to patients who could participate in the trial. Working with those sites, they may use various recruitment strategies, including patient databases, newspaper and radio advertisements, flyers, posters in places the patients might go (such as doctor's offices), and personal recruitment of patients by investigators. Volunteers with specific conditions or diseases have additional online resources to help them locate clinical trials. For example, the Fox Trial Finder connects Parkinson's disease trials around the world to volunteers who have a specific set of criteria such as location, age, and symptoms. Other disease–specific services exist for volunteers to find trials related to their condition. Volunteers may search directly on ClinicalTrials.gov to locate trials using a registry run by the U.S. National Institutes of Health and National Library of Medicine.[33]

2. Conclusion

When a drug is developed with evidence throughout its history of research to show it is safe and effective for the intended use in the United States, the company can file an application – the New Drug Application (NDA) – to have the drug commercialized and available for clinical application. NDA status enables the FDA to examine all submitted data on the drug to reach a decision on whether to approve or not approve the drug candidate based on its safety, specificity of effect, and efficacy of doses. The risk information seeking and processing (RISP) model analyzes social implications that affect attitudes and decision making pertaining to clinical trials. People who hold a higher stake or interest in the treatment provided in a clinical trial showed a greater likelihood of seeking information about clinical trials. Cancer patients reported more optimistic attitudes towards clinical trials than the general population. Having a more optimistic outlook on clinical trials also leads to greater likelihood of enrolling.

Compliance with ethical standards

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There is no conflict of interest.

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