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OF SCIENCES AND LITERATURE

Investigating Exploration: Understanding the Effect Of Population's General Knowledge on Clinical Trials as a Factor of Slow Recruitment as a Common Challenge in Clinical Studies

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A DISSERTATION

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Declaration

I do hereby attest that I am the sole author of this project/thesis and that its contents are only the result of the readings and research I have done.

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Abstract

Clinical Trial Professionals agrees that one of the biggest challenges in common during clinical trial execution is how to reduce the recruitment period during a clinical study. According to my Dissertation, one major element of this complex question is not Sponsor dependent. Despite of the efforts Companies put in clinical trial execution they cannot influence the willingness of Subjects to be a study participant.

According to my experience one major element of this issue is the lack of knowledge of the population on general drug research and development including clinical trials. This lack of knowledge may come either if not all from the following factors:

- lack of background knowledge on drug development
- unreliable sources of information
- lack of trust based on different factors
- myths around drug development
- contradictory information

My research consists of 2 parts. First, I developed a questionnaire to assess the general knowledge on clinical studies including the willingness of subject participation. Second contains the evaluation and statistical analysis of the data from around 60-200 participants.

My research also intends to find out the possibilities and give recommendations on how to implement the results to improve the population's general knowledge on R&D including Clinical Trials.

I. Drug research

History of Clinical Trials

The history of drug research has a long and fascinating history. Moreover, the full story is much longer than is documented. The willingness of humankind to cure diseases maybe coded in our genes and in the beginning, it is more experimental.
Almost every nation or tribe has its own way to cure diseases, mainly based on herbs like willow tree for arthritis, ginger for intestinal problems and immune system booster. Traditionally, tribal knowledge has been passed on from one generation to the next through oral communication. The tradition is now on the wane as the new generation moves away from the tribal cultures and habitats. The names and terminologies used by the tribes for plants are region-specific, and the undocumented information might be lost forever.

Luckily, some of the Orders (like Benedictine Order) were keen to document the knowledge coming from the past to preserve it for the future.

Most probably the first documented clinical trial can be found in the Holy Bible. The Book of Daniel (2nd Century BC).

This was an experiment resembling a modern clinical trial. This experiment was not conducted by a medical professional, but by King Nebuchadnezzar's "Chief of Staff" called Melzar. According to the King's rule in Babylon, people must eat only meat and drink only wine, a diet he believed would keep them in fresh physical condition. But Daniel, who preferred to eat vegetables (according to his belief), refused to keep to the King's dietary requirement. The "Chief of Staff", Melzar allowed their own diet of vegetables (mainly legumes) and water — but only for 10 days. When the experiment ended, the vegetarians appeared better nourished than the meat-eaters, so the king finally permitted the vegetarians to continue their diet. This was probably the one of the first times in the evolution of the human species that an open uncontrolled human experiment guided a decision about public health.

James Lind is considered the first physician to have conducted a controlled clinical trial of the modern era. Dr Lind (1716-94), whilst working as a surgeon on a ship, was appalled by the high mortality of scurvy amongst the sailors. He planned a comparative trial of the most promising cure for scurvy. His vivid description of the trial covers the essential elements of a controlled trial.

As Lind took in his notes:" On *the 20th of May 1747, I selected twelve patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of the knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all, viz. water gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times light puddings, boiled biscuit with sugar, etc., and for supper, barley and raisins, rice and currants, sago and wine or the like. Two were ordered each a quart of cyder a day. Two others took twenty-five drops of elixir vitriol three times a day … Two others took two spoonfuls of vinegar three times a day … Two of the worst patients were put on a course of seawater … Two others had each two oranges and one lemon given them every day … The two remaining patients, took … an electuary recommended by a hospital surgeon … The consequence was, that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them, being at the end of six days fit for duty … The other was the best recovered of any in his condition; and … was appointed to attend the rest of the sick. Next to the oranges, I thought the cyder had the best effects …"* (Dr James Lind's "Treatise on Scurvy" published in Edinburgh in 1753)[3, 4, 7, 17]

The results were clear and supported today's widely known fact that scurvy caused by the lack of Vitamin C and can be cured and prevented by Vitamin C intake.

Today in most clinical trials aiming novel therapy the placebo is imperative element. The word placebo first appeared in medical literature in the early 1800s. Hooper's Medical Dictionary of 1811 defined it as "an epithet given to any medicine more to please than benefit the patient." However, it was only in year 1863 that United States physician Austin Flint planned the first clinical study comparing a dummy remedy to an active treatment. He treated thirteen patients suffering from rheumatism with an herbal extract which was advised instead of an established cure. In 1886, Flint described the study in his book: A Treatise on the Principles and Practice

of Medicine. “This was given regularly and became well known in my wards as the ‘placeboic remedy’ for rheumatism. The favorable progress of the cases was such as to secure for the remedy generally the entire confidence of the patients.”[3,4,7]

The Medical Research Council (MRC) UK carried out a trial in 1943-4 to investigate patulin treatment for (an extract of Penicillium Patulinum) the common cold. This was the first double blind comparative trial with concurrent controls in the general population in recent times. It was one of the last trials with non-randomized or quasi-randomized allocation of subjects. The MRC Patulin Clinical Trials Committee (1943) was chaired by Sir Harold Percival Himsworth, and its statisticians were M Greenwood and W J Martin. This nationwide study enrolled over a thousand British blue- and white-collar workers suffering from colds.

The study was rigorously controlled by keeping the physician and the patient blinded to the treatment. The treatment allocation was done using an alternation procedure. A nurse allocated the treatment in strict rotation in a separate room. The nurse filed the record counterfoil separately and detached the code label for the appropriate bottle before asking the patient to visit the doctor. The statisticians considered this an effective random concurrent allocation. However, the outcome of the trial was disappointing as the analysis of trial data did not show any protective effect of patulin.

The idea of randomization was introduced in 1923. However, the first randomized controlled trial of streptomycin in pulmonary tuberculosis was carried out in 1946 by MRC of the UK. The MRC Streptomycin in Tuberculosis Trials Committee (1946) was chaired by Sir Geoffrey Marshall, and the statistician was Sir Austin Bradford Hill and Philip Hart, who later directed the MRC's tuberculosis research unit, served as secretary. Marc Daniels, as the “registrar” coordinated the clinicians at the participating hospitals. The trial began in 1947. As the amount of streptomycin available from US was limited, it was ethically acceptable for the control subjects to be untreated by the drug—a statistician's dream. This trial was a model of meticulousness in design and implementation, with systematic enrolment criteria and data collection compared with the ad hoc nature of other contemporary research a key advantage of Dr Hill's randomization scheme over alternation procedure was “allocation concealment” at the time patients were enrolled in the trial. Another significant feature of the trial was the

use of objective measures such as interpretation of x-rays by experts who were blinded to the patient's treatment assignment.[3,4,7]

Sir Bradford Hill had formed his allocation ideas over several years (with randomization replacing alternation to better conceal the allocation schedule) but had only tried them out in disease prevention. Dr Hill instituted randomization – a new statistical process which has been described in detail in the landmark BMJ paper of 1948.

“Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case) was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each center by Professor Bradford Hill; the details of the series were unknown to any of the investigators or to the co-coordinator and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number. After acceptance of a patient by the panel, and before admission to the streptomycin center, the appropriate numbered envelope was opened at the central office; the card inside told if the patient was to be an S or a C case, and this information was then given to the medical officer of the center. Patients were not told before admission that they were to get special treatment. C patients did not know throughout their stay in hospital that they were control patients in a special study; they were in fact treated as they would have been in the past, the sole difference being that they had been admitted to the center more rapidly than was normal. Usually, they were not in the same wards as S patients, but the same regime was maintained.”[3,4,7]

Sir Bradford Hill had been anxious that physicians would be unwilling to give up the doctrine of anecdotal experience. However, the trial quickly became a model of design and implementation and gave a boost to Dr Hill's views and subsequent teaching, and resulted, after some years, in the present virtually universal use of randomized allocation in clinical trials. The greatest influence of this trial lay in its methods which have affected virtually every area of clinical medicine. Over the years, as the discipline of controlled trials grew in sophistication and influence, the streptomycin trial continues to be referred to as groundbreaking.[3,4,7]

Today clinical trials are guided by rules, regulations, and authorities’ s guidance which are continuously evolving. These rules have two major intentions. First to protect the human

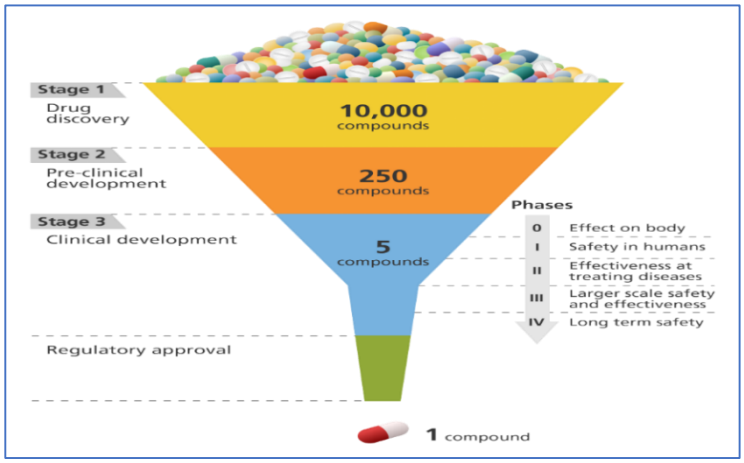
rights and well-being enrolled in clinical trials and second to protect clinical trial data integrity in order. Nowadays, participation in clinical trials is safe.

Why are the original medicines pricy?

If we compare the prices of the original medicines with the generics it is clearly visible there is a significant difference. The original medicines are much pricier than generics. Why is this difference? Where is it coming from? The short answer is that the price of an original medicine includes the cost of the development process while the generic medicine does not.

To see the full picture, we should understand the drug discovery process, which is long, pricy, and full of points where the drug candidate can fail. Drug Discovery involves many different phases, processes, which start with an idea comes from an unmet medical need where the drug candidate/molecule became an approved medicine through a long and well-regulated journey under the control of different Regulatory Authority (FDA, EMA, National Authorities supervised by Ethics Committees. Do not forget that an active compound can said to be a safe drug only after in-depth examination and intensive studies.

The evidence shows that an average medicine's development time takes 10-15 years and costs around 2.6 billion USD (PhRMA, 2023). Above of this only one out of every 5000-10000 molecule can reach to the market as approved medicine. It means that most of a molecule/compound ever discovered never became a medicine. Once a molecule became a medicine the pharmaceutical companies obliged to perform post-marketing surveillance which gives an additional 300 million USD so the final cost of the development could go up to 3 billion USD.

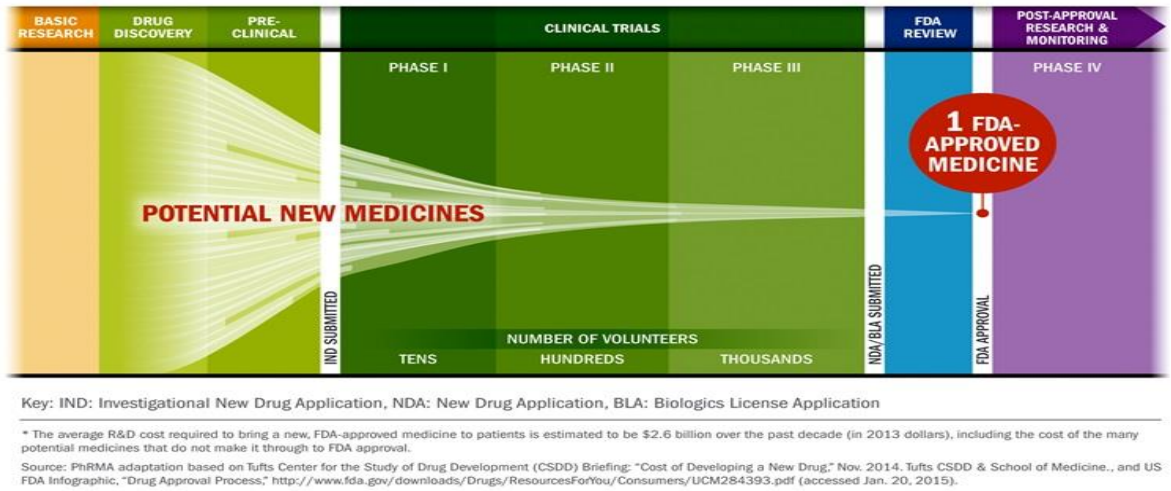


2. FIGURE, STAGES OF CLINICAL TRIALS BY COMPOUND LOST, IMAGE CREDIT: PNGKEY.COM

So, this lengthy process needs a significant investment in money, time and working hours which should return within the lifecycle of an original medicine until the patent is expired and generics will appear.

Drug Discovery

The Drug Discovery Process involves many different actions and testing. Researchers collaborate to identify and optimize potential leads to a specific target. Essentially, the leads must elicit a desirable effect on a specific biological target implicated in a disease, in the hopes of treating it.



2. FIGURE, DRUG DISCOVERY PROCESS BY TIME SPENT, IMAGE CREDIT PHRMA BASED ON FDA GRAPH BY GOA

Most of a new drug start with a medical indication where either no or no effective treatment is available. What does it mean in the practice? There is simply no treatment available. There is available treatment, but it is limited to a group of patients. It is also possible that the therapy is exists and is available for all patients, but the existing therapy is outdated or could be better in terms of working better (efficacy) or has a better safety profile (e.g., targeted tumor cells) or it has better compliance (e.g., once a day tablet versus subcutaneous injection).

Once it is done the goal is to discover all target for the disease.

Since human DNA was sequenced, reverse pharmacology has found remedies to existing diseases through modern testing.

Disease processes, molecular compound tests, existing treatments with unanticipated effects, and innovative technologies spur drug discovery timeline through the cycle below.

Today the steps in drug discovery and development involve screening hits, iterative medicinal chemistry, and optimization of hits to reduce potential drug side effects (increasing affinity and selectivity). Efficacy or potency, metabolic stability (half-life), and oral bioavailability are also improved in these steps of the drug development process.

Target Identification and Validation

Target identification finds a gene or protein (therapeutic agent) that plays a significant role in a disease. Afterward, scientists and researchers record the target's therapeutic characteristics. Drug targets must be efficacious, safe, usable, and capable of meeting clinical and commercial requirements. To validate targets, researchers use modern tools and techniques such as disease association, bioactive molecules, cell-based models, protein interactions, signaling pathways analysis, functional analysis of genes, in vitro genetic manipulation, antibodies, and chemical genomics. For example, Genome CRISPR libraries and Duolink PLA (Proximity Ligation Assay) are excellent sources for drug discovery targets.

Hit Discovery Process

Following target validation, compound screening assays are developed.

Assay Development and Screening

Assay development in drug discovery is a crucial component of drug discovery workflow. Assays are test systems that evaluate the effects of the new drug candidate at the cellular, molecular, and biochemical levels.

High Throughput Screening

High Throughput Screening (HTS) uses robotics, data processing/control software, liquid handling devices, and sensitive detectors to rapidly conduct millions of pharmacological, chemical, and genetic tests, eliminating hours of painstaking testing by scientists. HTS identifies active compounds, genes, or antibodies that affect human molecules.

Hit To Lead

In the Hit to Lead (H2L) process, small molecule hits from an HTS are evaluated and optimized in a limited way into lead compounds. These compounds then move on to the lead optimization process.

Lead Optimization

In the lead optimization (LO) process, the lead compounds discovered in the H2L process are synthesized and modified to improve potency and reduce side effects. Lead optimization conducts experimental testing using animal efficacy models and ADME tools, designing the drug candidate.

Preclinical research

Once a lead compound is found, preclinical phase of drug development begins with in vivo research to determine the efficacy and safety of the drug. Researchers determine the following about the drug:

- Absorption, distribution, metabolization, and excretion information
- Potential benefits and mechanisms of action
- Best dosage, and administration route
- Side effects/adverse events

- Effects on gender, race, or ethnicity groups
- Interaction with other treatments
- Effectiveness compared to similar drugs

Preclinical Trials assess the new drug on non-human subjects for efficacy, toxicity, and pharmacokinetic (PK) information. Scientists conduct these trials in vitro and in vivo with unrestricted dosages.

Absorption, Distribution, Disposition, Metabolism, & Excretion

Absorption, Distribution, Disposition, Metabolism, & Excretion (ADME) is a Pharmacokinetic (PK) process of measuring the ways the new drug affects the body. ADME involves mathematical descriptions of each effect.

Proof of Principle / Proof of Concept

Proof of Principle (PoP) are studies that are successful in preclinical trials and early safety testing. Proof of Concept (PoC) terminology is used almost interchangeably with PoP in drug discovery and development projects. Successful PoP/PoC studies lead to program advancement to the Phase II studies of dosages.

In Vivo, In Vitro, and Ex Vivo Assays

These three types of studies are conducted on the whole, living organisms or cells, including animals and humans: or using non-living organisms or tissue extract. In vivo, preclinical research examples are the development of new drugs using mice, rat, and dog models. In vitro is research conducted in a laboratory. Ex vivo uses animal cells or tissues from a non-living animal. Examples of ex vivo research assays are finding effective cancer treatment agents; measurements of tissue properties (physical, thermal, electrical, and optical); and realistic

modeling for new surgical procedures. In an ex vivo assay, a cell is always used as the basis for small explant cultures that provide a dynamic, controlled, and sterile environment.

In Silico Assays

In silico assays are test systems or biological experiments performed on a computer or via computer simulation. These are expected to become increasingly popular with the ongoing improvements in computational power, and behavioral understanding of molecular dynamics and cell biology.

Drug Delivery

New drug delivery methods include oral, topical, membrane, intravenous, and inhalation. Drug delivery systems are used for targeted delivery or controlled release of new drugs. Physiological barriers in animal or human bodies may prevent drugs from reaching the targeted area or releasing when they should. The goal is to prevent the drug from interacting with healthy tissues while still being effective.

Oral: Oral delivery of medications is reliable, cost-effective, and convenient for patients. Oral drug delivery may not monitor precise dosages to the desired area but is ideal for prophylactic vaccinations and nutritional regimens. Delayed action, stomach enzyme destruction, absorption inconsistencies, or patients with gastrointestinal issues or upset stomach can occur, and patients must be conscious during administration.

Topical: Topical drug delivery involves ointments, creams, lotions, or transdermal patches that deliver a drug by absorption into the body. Topical delivery is more useful for patient with skin or muscular conditions — patients prefer it due to non-invasive delivery and their ability to self-administer the medicine.

Parenteral: (IM, SC, or LP Membrane) Parenteral drug delivery utilizes bodily membranes, including intramuscular (IM), intraperitoneal (IP), or subcutaneous or (SC). It is often used for unconscious patients and avoids epithelial barriers that are difficult for drugs to cross.

Parenteral: (Intravenous) Intravenous injection is one of the fastest drug delivery absorption methods. IV injection ensures entire doses of drugs enter the bloodstream, and it is more effective than IM, SC, or LP membrane methods.

Parenteral: (Inhalation) Inhalation drug delivery gets the drug rapidly absorbed into the mucosal tissue of lungs, nasal passages, throat, or mouth. Problems with inhalation includes difficulty delivering the optimum dosage due to small mucosal surface areas and patient discomfort. Pulmonary inhalation drug delivery uses fine drug powders or macromolecular drug solutions. Lung fluids resemble blood, so they can absorb small particles easily and deliver them into the bloodstream.

Formulation Optimization & Improving Bioavailability

Formulation optimization is ongoing throughout pre-clinical and clinical stages. It ensures drugs are delivered to the proper place at the right time and in the right concentration.
As a summary before evaluating a drug in humans, it must undergo non-clinical testing to obtain basic toxicity and pharmacological data. Non-clinical testing must include animal models and assays to explore pharmacology, toxicity, reproductive toxicity, and genotoxicity. Preclinical development can take anywhere from 1-4 years and may require further testing to be in conjunction (or in parallel) with clinical studies.

The Objectives of Preclinical Development:

1. Identifying the physical and chemical properties of the candidate drug
2. Testing the candidate drug in vitro
3. Determining formulation for administration to test subjects and patients
4. Developing manufacturing methods for the candidate drug

5. Testing the candidate drug in cultured cells
6. Assessing the candidate drug in animals for safety
7. Developing analytical assays
8. Securing intellectual property protection for the potential product, its uses, and its manufacture

ADME (Absorption, Dissemination, Metabolic, Excretion)

For a potential drug to be useful, it must be stable, safe, and be manufactured practically. This stage is also dedicated to determining the drug's activity, chemical attributes, and solubility and outlining manufacturing schemes to ensure its potential as a drug. If the drug shows potential in the laboratory, the next step requires toxicity tests. These tests are also known as ADME (Absorption, Dissemination, Metabolic, and Excretion) studies**.** ADME studies are conducted on animals and help researchers determine:

- How much of the drug is absorbed by the blood?
- How is the substance metabolically altered in the body?
- What are the toxicity effects of metabolic by-products?
- How quickly will the drug and its by-products be excreted?

Toxicity

Safety assessment is done using toxicity studies. These studies are conducting using Good Laboratory Practice (GLP) guidelines for 30-90 days, in a minimum of two mammalian species, one of which must be non-rodent. The dosage, length of study, and complexity of study are related to the proposed clinical study; duration and complexity should be equal to or exceed what is proposed in humans. Additionally, if the new drug is also a New Chemical Entity (NCE) and has no long-term human data at all, the study may be required to exceed 12 months.

- **Reproductive Toxicity**. Fertility and embryonic development are also studied extensively in human clinical trials. This includes early embryonic development, embryo-fetal development, as well as pre- and post-natal development.

- **Genotoxicity**. Genotoxicity, the propensity to damage genetic information, is also extensively studied in both in-vitro and in vivo. This assessment of mutagenicity is evaluated in both bacteria and mammalian cells.
- **Carcinogenicity**. Carcinogenicity studies are not required before clinical studies begin and may not have to be done for some products. These studies may take upwards of 2 years to complete.

This entire process takes an average of 5 years.

II. Drug Development

Translation Medicine in Clinical Drug Development

By default, translational medicine is the return of the results of basic research and clinical research, and more specifically, all kinds of research results (basic research, meta-analysis, cohort analysis, clinical research) back to patient care as soon as possible.

Translational medicine thus includes the utilization of the following in patient care:

- basic research experiments to understand the development of diseases,
- finding drug attack points and assessing their effectiveness in human therapies,
- biological examination of human diseases,
- new developments in the treatment of human diseases,
- non-human or non-clinical studies that may form the basis of new clinical applications in the future,
- drug development experiments in Phase 1-3 clinical studies,
- meta-analyses,
- cohort analyses,
- observational and randomized clinical trials.

This combination of theoretical and clinical, basic research and healing potential, as well as translational thinking itself should be a new way to be used for the future.

Why is a Center for Translation Medicine needed?

The approach based on translational medicine does not mean a new system, but a return - of course, to the 20th century, reconsidered in a 21st century way – to the roots. In the 1950s, the clinical systems were structured in such a way that clinical examinations, healing activities, and theoretical research were combined, and the members of the research groups performed in all areas. The development of the following decades and the specialization of research areas resulted in the separation of clinical (e.g., internal medicine, surgery) and theoretical (e.g., physiology, molecular biology) research. By the end of the 20th century, this separation became one of the greatest challenges of medicine. In many cases, the two areas no longer even understand each other. Despite billions of dollars more being spent on theoretical and

pharmaceutical research worldwide, the number of products/medicines that can be used in patient care has not increased. It is an often-quoted fact that only a small fraction of tens of thousands of candidate drug molecules, roughly a thousand molecules, make it to the stage to preclinical testing.

Once again, the translational model links the systems of clinical and basic research together in a targeted search for answers to questions that arose during patient care in the clinic, thus resulting in a noticeable improvement in the health of the population.

One of the main advantages of the system is that basic research results can be immediately converted into clinical application, different research/treatment areas can be separated. Clinical medicine can be divided into two main categories: general and translational medicine. The main tasks of the general part would be primarily on primary care and graduate training, while the translational part would primarily be on clinically oriented basic research, clinical trials (increasing scientific output), pharmaceutical phase trials (discovering new therapy and, in addition, increasing institutional income) and postgraduate training (increasing the number of PhD and other academic doctoral degrees). The patient could only be included in the translational part if he/she agrees to participate in a clinical trial.

Another feature of the system is its multidisciplinary nature, i.e., by coordinating the different fields of science (informatics, statistics, data management, general management, and administration) it operatively supports the theoretical and clinical research of individual medical fields.

The cornerstone of translational medicine is the registration system covering all clinical areas and the related biobank. Its expansion is ensured by the appropriate info-communication background. They are started, uploaded, managed, and each other's data is used according to strict legal and ethical principles. This makes it possible to have a sufficient number of cases available for the clinical trials that have been started, which can provide serious evidence for the understanding and treatment of individual diseases and can increase the scientific value of the future communication.

The best international centers of translational medicine, where the translational approach to medicine was first institutionalized, are the National Institute of Health (NIH) and the Harvard Clinical and Translational Science Center. Today such centers can be found in, for example,

Cambridge and Oxford and they control most of the world's research potential, and their publications appear in the most important scientific journals.

With the successful completion of the laboratory development (so-called: preclinical phase), the human trials can begin. In general, clinical trials can be classically divided into four categories.

Investigational preparation is being used in humans for the first time in Phase I studies. Phase I clinical trials can be separated into two subgroups: I/a and I/b. The purpose of subgroup I/a is to examine whether the active ingredient be used safely in humans, what side effects occur, and what is the pharmacokinetics of the active substance in the body (how it is absorbed, broken down, excreted who etc.). During Phase I/a. a fraction of the animal experimental doses are used in the study. The Phase I/b. examination subgroup is similar to I/a, but one or more doses are repeated in one or more dosages. In Phase I trials (except for oncology drugs) healthy volunteers take part, who receive predetermined remuneration for their participation.

During Phase II. studies the active substance is used on patients for the first time in studies. Apart of Phase I. study goals, the pharmacological effect of the active substance becomes important here, i.e., its examination of how the drug affects the human body. In these trials generally small number, typically 100-300 carefully selected patients are involved. An important result of this phase is selection of a dose that seems optimal for further examination during Phase III. clinical studies

If the early phase tests are successful, the registration trials so called Phase III studies will begin, where the main goals are the detailed verification of the effect of the investigational product, the indication areas mapping and gaining knowledge about less common side effects. Phase III trials typically carried out in several centers (multicenter), in several countries (multinational), involving thousands of patients and last the longest period comparing to Phase I and Phase II studies.

The result of Phase III studies, in the best case, is the registration of the active ingredient, and finally the molecule becoming a medicine.

Phase IV clinical trials now involve an already registered medicine. There are several purposes of these kind of trials: application in special patient groups (e.g., patients with already existing

comorbidities, such as lung or kidney), new indication mapping of areas, further clarification of the drug's side effect profile. It worth to mention that EU Commission is moving away from Phase IV studies due to novel protocol design described later in my Thesis.

There are so called Non-interventional (NI) trials but those must be separated from the phase I-IV trials. Throughout the course of NI trials, the medicine must be used according to the official Summary of Product Characteristic (SMPC) with indication and conditions (dose, frequency of use), and only those examinations can be performed (laboratory, imaging, etc.), which is necessary anyway due to the illness characteristic. Their goal is long-term applicability assessment, side effect data collection, compliance, quality of life, measurement of resource use and cost data, in the widest possible range of patients under the conditions of routine daily practice.

Bioequivalence studies are conducted on the generic drug candidate and represent the comparative pharmacological testing of an original preparation, the prerequisite for the registration of generic drugs.

Ethical background

Clinical trials with investigational products are part of medical research which is conducted with active ingredients. The legislator also separates medical research and clinical trials when developing regulations, as well as for practical reasons, the group of examinations not involving intervention. From the point of view of this dissertation, the rules of medical research are essential as they provide a general framework for clinical and non-interventional studies.

Content elements of international and domestic legislation on clinical trials are essentially fed by two principal sources: one by the ethics of research conducted on humans is made up of a group of international regulations and recommendations, the other is research its practical implementation: planning, organization, execution, documentation and consist of recommendations and guidelines formulating its control and quality assurance. The two

sources of course, is intertwined at many points, presupposes and results from each other, since it can be clearly seen that both the cause and the consequence of the ethics of the research are high quality standards, careful planning, and accurate documentation.

The 10 points of the Nuremberg Code, which can be considered one of the first unified formulations of ethical principles, and the Geneva Declaration of 1948 appeared together in 1964 and was later amended several times (the last time in 2017) in the Declaration of Helsinki. The Council of Europe referring to previous international declarations, conventions, and charters on the protection of human rights and dignity related to the application of medical science agreement was laid down in 1997, which became known as the Oviedo Convention named after the place of signing the document. In 2005, a Protocol on Biomedical Research was also attached.

Good Clinical Practice (the English formed from the name and with a widely spread abbreviation: GCP) is partly created by the USA "Food, Drug and Cosmetic" law, partly to WHO's scientific working groups, which are specifically created to lay down the basic principles of investigation procedures. After establishing the principles within a relatively brief period of time, widespread systems of rules were created in the world, which, was however against the unification of the pharmaceutical market, and thus the need of uniform regulation. The "International Conference on Harmonization (ICH)" was developed between 1990-96 by the unified system of rules known today as ICH-GCP, which is used worldwide are accepted by the competent authorities. The ICH-GCP is adopted by the European Parliament. It should be noted that there are a different “Good Practices” which must also be met when conducting a clinical trial such as the Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) guidelines.

In order to safeguard the human right and wellbeing of the patients involved in clinical trials Ethics Committees engage in the evaluation and approval process of clinical trials.

Legal background

The whole medicine development process is well regulated and harmonized. The accepted basis for the conduct of clinical trials in humans founded in the protection of human rights

and the dignity of the human being with regards to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. The clinical trial subject's protection safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by Ethics Committees and Member States's competent authorities, and rules on the protection of personal data.

FDA

FDA (Food and Drug Administration, US) protecting the rights, safety and welfare of people who participate in clinical trials. It is a critical aspect of the FDA's mission. FDA oversees clinical trials to ensure they are designed, conducted, analyzed, and reported according to federal law and good clinical practice (GCP) regulations. FDA's regulations and guidelines for clinical trials support efficient medical product development, while assuring trials generate the robust evidence needed to assess product safety and efficacy. The agency works to ensure its GCP policies continue to facilitate novel approaches to generating quality clinical evidence.
For this reason, FDA issued many so-called Clinical Trial Guidance Documents which describe the FDAs thinking on how a clinical study must be conducted. The researchers obliged to comply with these documents, rules, and regulations.

EUROPEAN UNION

European Union (EU) pharmaceutical legislation known as the Clinical Trials Regulation entered into application on 31 January 2022. It aims to ensure the EU offers an attractive and favorable environment for carrying out clinical research on a large scale, with high standards of public transparency and safety for clinical trial participants.
On 31 January 2022, the Regulation repealed the Clinical Trials Directive (EC) No. 2001/20/EC and national implementing legislation in the EU Member States, which regulates clinical trials in the EU until the Regulation's entry into application.
The Clinical Trials Regulation harmonizes the processes for assessment and supervision of clinical trials throughout the EU.

The evaluation, authorization and supervision of clinical trials are the responsibilities of EU Member States and European Economic Area (EEA) countries.

Prior to the Regulation, clinical trial Sponsors had to submit their Clinical Trial Applications separately to National competent authorities and Ethics Committees in each country to gain regulatory approval to run a clinical trial.

The Regulation enables sponsors to submit one online application via a single online platform known as the Clinical Trials Information System (CTIS) for approval to carry out a clinical trial in several European countries, making it more efficient to perform such multinational trials.

The Regulation also makes it more efficient for EU Member States to evaluate and authorize such applications together, via the Clinical Trials Information System.

The purpose is to foster innovation and research in the EU, facilitating the conduct of larger clinical trials in multiple EU Member States/EEA countries.

Other key benefits of the Regulation include:

- improving information-sharing and collective decision-making on clinical trials;
- increasing transparency of information on clinical trials;
- ensuring high standards of safety for all participants in EU clinical trials.

EU also has a set of documents so called EudraLex – Volume 10 **„**The rules governing medicinal products in the European Union" contains guidance documents applying to clinical trials.[13]

NATIONAL LAWS AND REGULATIONS

Beside of FDA's and EU Member State's every Country has its own set of rules and regulations how a clinical study conducted and can be vary in terms of Regulatory/Ethics approval process and it is not aim of this dissertation to list all of them.

Content elements of international and domestic legislation on clinical trials they are essentially fed by two principal sources: one by the ethics of research conducted on humans is built up of a group of international resolutions and recommendations, the other is research its practical implementation: planning, organization, implementation, documentation, in line with recommendations and guidelines formulating its control and quality assurance. The two sources of course, is intertwined at many points, presupposes and results from each other,

since it can be clearly seen that both the cause and the consequence of the ethics of the research are in high quality standards, carefully planned, and accurately documented.

Phase 0 trials – Microdosing

During Phase 0 trials investigational product is tested in a small number of humans using a very small dose of medication to make sure it isn't harmful to humans before using it in higher doses for later phases.

Phase 0 trials are conducted without therapeutic intent. Subtherapeutic yet pharmacologically effective drug doses are administered to study participants, who may be either patients or healthy volunteers. The amount of time that participants are exposed to the agent is restricted, but dose escalation is permitted as long as the goal is not to establish a safety/toxicity profile. The FDA permits more constrained (single-dose or short-course) preclinical toxicology studies to be performed to establish margin of safety rather than dose-limiting toxicities because low doses and drug exposures do not foresee severe drug-related adverse outcomes. Furthermore, full-scale, clinical good manufacturing practice-grade commercial manufacturing is not necessary prior to trial beginning due to the little amount of study drug required to run a Phase 0 trial. Phase 0 trials can therefore be started far earlier in the clinical development of an investigational product than standard phase I studies, offering a valuable chance to examine PK and drug target effects in people much earlier. Such pilot trials with a limited number of patients can provide information that can help with clinical development decisions and improve the design of subsequent trials.

The guidelines define micro doses as less than 1/100th of the amount determined to have a pharmacologic impact in preclinical animal toxicology investigations, up to a maximum of 100 mg (or no more than 30 nmol for protein products). Preclinical toxicological studies completed to support the exploratory IND should show that a dose one hundred times greater than the suggested clinical dose does not result in adverse effects in real-world situations. Comparatively, the beginning dose for a first-in-human oncology study carried out under a standard IND may be 1/10th of the dose that caused serious toxicity or death in 10% of the studied animals.

Phase 0 trials typically require only 10 to 15 individuals, which is less than a phase I study because the focus is on proof-of-concept rather than finding a dose to employ in phase II testing based on toxicity. Based on the FDA guidelines the duration of Phase 0 is a maximum of 7 days, however some flexibility can be considered.

Summary:

- Micro dosing study: Less than 1/100 of standard dose
- Limited dosing (1-7 days)
- Evaluate a small dose of the drug in a small number of people (<15)

Phase 1 trials – testing for Safety and Dosage

Small groups of 20-100 healthy volunteers are typically recruited. These studies are often conducted in clinical trial clinics or Phase I Units where full-time staff can observe subjects. These clinical trial clinics are often run by Pharmaceutical Companies, Contract Research Organizations (CROs) who conduct these trials on behalf of pharmaceutical companies and other researchers. Drug-administered subjects are usually observed until several half-lives of the drug have passed. This phase helps assess drug safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics. Phase 1 trials typically involve dose-finding studies, also called dose escalation studies, to find the optimal and safest dose and to discover when a compound is too toxic to administer. The dose range assessed is typically the fraction [quantified] of the dose that caused harm in animal studies. Phase I trials include primarily healthy subjects. However, there are situations in which clinical patients are involved, such as: Patients with terminal cancer or HIV whose treatment can make healthy people sick. These studies typically conducted in tightly controlled clinics called CPUs (Central Pharmacological Units), where the participant receives her round-the-clock medical care and monitoring. In addition to the patients already mentioned, phase I trials may also include “patients who are usually unsuccessful in trying to improve existing standard of care”. Volunteers receive a variable fee for time spent at the Volunteer Center. Prior to initiating Phase I trials, sponsors must submit to the FDA a New Drug Application detailing preliminary drug data collected from cell models and animal studies.

Single ascending dose (Phase 1a)

In single ascending dose studies, small groups of subjects are given a single dose of the drug while they are observed and evaluated for a period of time to confirm safety. Typically, a small number of participants, usually three, are entered sequentially at a particular dose. If they do not exhibit any adverse side effects, and the pharmacokinetic data are roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. If unacceptable toxicity is observed in any of the three participants, an additional number of participants, usually three, are treated at the same dose. This continued until pre-calculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up (at which point the drug is said to have reached the Maximum Tolerated Dose (MTD)). If an additional unacceptable toxicity observed, then the dose escalation is terminated and that dose, or perhaps the previous dose, is declared to be the maximally tolerated dose. This particular design assumes that the maximally tolerated dose occurs when approximately one-third of the participants experience unacceptable toxicity. Several variations of this kind of design exist, but most are similar.

Multiple ascending dose (Phase 1b)

Multiple ascending dose studies investigate the pharmacokinetics and pharmacodynamics of multiple doses of the drug, searching for safety and tolerability. In these studies, groups of patients were given multiple low-dose investigational products, and samples (blood, urine, or other bodily fluids) were taken and analyzed at various times to provide insight into how the drug is being processed in the body. The repetitive dosing in Phase 1b study allows steady state to be reached, which is when the rate of drug absorption is equal to the rate of drug elimination thusly the concentration of drug in the body is in balance. Although steady state concentrations can be predicted from a single-dose study, a multiple-dose study provides empirical confirmation.

Food effect

A simple study that examines differences in drug absorption by meal before investigational product administration. These studies are usually conducted as crossover studies, in which volunteers receive two identical doses of the test article, fasted and fed.
Summary:

- Involves 10s subjects without the disease
- Aim to understand the fundamental pharmacokinetic (PK) and pharmacodynamic (PD) properties (including safety and tolerability) of the drug in human subjects
- Multiple Dose study
- Assess the intrinsic (e.g., age, genetics, disease) and extrinsic (e.g., food, other drugs) effects on drug levels in the human body

Phase 2 trials – testing to Efficacy and Safety

Once a dose or range of doses is determined, the next goal is to evaluate whether the drug has any biological activity or effect. Phase 2 trials are performed on larger groups (50–300) and are designed to assess how well the drug works, as well as to continue Phase 1 safety assessments in a larger group of volunteers and patients. Genetic testing is common, particularly when there is evidence of variation in metabolic rate. When the development process for a new drug fails, this usually occurs during Phase 2 trials when the drug is discovered not to work as planned, or to have toxic effects. Phase 2 studies are sometimes divided into Phase 2a and Phase 2b. There is no formal definition for these two sub-categories, but generally Phase 2a is a proof-of-concept (PoC) and Phase 2b is dose ranging studies. Phase 2a studies are usually pilot studies designed to demonstrate clinical efficacy or biological activity. Phase 2b studies determine the optimal dose at which the drug shows biological activity with minimal side-effects (so called 'definite dose-finding' studies).

Trial design

Some Phase 2 trials are designed as case series, demonstrating a drug's safety and activity in a selected group of participants. Other Phase 2 trials are designed as randomized controlled trials, where some patients receive the drug/device and others receive placebo/standard treatment. Randomized Phase 2 trials have far fewer patients than randomized Phase 3 trials. In the first stage, researchers try to exclude drugs that have little or no biological activity. For example, a researcher may specify that a drug must have a certain minimum level of activity. For example, her 20% of participants. If the estimated activity level is less than 20% of hers, the investigator chooses not to consider the drug further, at least at this maximum tolerated dose. If the estimated activity level exceeds 20%, the researchers add more participants to better estimate the response rate. Excluding a response rate of 20% or less, a typical study enrolls 14 participants. If the first 14 participants fail to respond, the drug is considered to have an activity level of 20% or greater. The number of participants added can range from 10 to 20, depending on the level of accuracy desired. Therefore, in a typical phase II cancer study, he may include fewer than 30 people to estimate response rates. When efficacy is assessed in a study, a drug administered in a particular manner as described in the study should be tested in selected populations (e.g., cancer patients with no other pre-existing disease) for the endpoint of interest (e.g.: tumor size). can influence. When studies assess efficacy, they determine whether a treatment affects disease. In efficacy studies, it is important to treat participants as if the treatment were prescribed in the clinic. This means that there should be no aspect of the study designed to increase compliance beyond what occurs in normal clinical practice. more generally applicable than (e.g., in efficacy studies, patients may feel better, visit fewer hospitals, as opposed to better test scores or lower cell counts; and live longer). Efficacy studies typically have less tight control over participant types than efficacy studies. This is because researchers are interested in whether a drug has broad effects in a population of patients with the disease.

According to FDA approximately 33% of drugs move to the next phase.

Summary:

- At this step you evaluate the drug in a limited group of patients (10s – 100s) with the disease or condition for which the drug was developed
- Determine the optimal dose for the drug (dose at which there is maximum effect with the minimum number of adverse effects)
- Determine the therapeutic dose range for the drug + safety
- Distinguish Phase 2a (proof of concept) and Phase 2b (dose ranging)
    - Phase 2a = 20-100 patients
    - Phase 2b = 80-500 patients

Phase 3 trials – Clinical Testing of Efficacy and Monitoring of Adverse Reactions

This phase is designed to assess the effectiveness of the new intervention and, thereby, its value in clinical practice. Phase 3 studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase 3 trials are the most expensive, time-consuming, and difficult trials to design and run, especially in therapies for chronic medical conditions. Phase 3 trials of chronic conditions or diseases often have a short follow-up period for evaluation, relative to the period of time the intervention might be used in practice. This is sometimes called the "pre-marketing phase" because it actually measures consumer response to the drug.

It is widespread practice that certain Phase 3 trials will continue while the regulatory submission is pending at the appropriate regulatory agency. This allows patients to continue to receive possibly lifesaving drugs until the drug can be obtained by purchase. Other reasons for performing trials at this stage include attempts by the sponsor at "label expansion" (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug. Studies in this phase are by some companies categorized as "Phase 3b studies."

While not required in all cases, it is typically expected that there be at least two successful Phase 3 trials, demonstrating a drug's safety and efficacy, in order to obtain approval from the appropriate regulatory agencies such as FDA (US), or the EMA (European Union).

Once a drug has proved satisfactory after Phase 3 trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to the appropriate regulatory authorities in different countries. They will review the submission, and if it is acceptable, give the Sponsor approval to market the drug.

Most drugs undergoing Phase 3 clinical trials can be marketed under FDA norms with proper recommendations and guidelines through a New Drug Application (NDA) containing all manufacturing, preclinical, and clinical data. In case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase 3 clinical trials in the market.

Adaptive design

The design of individual trials may be altered during a trial – usually during Phase 2 or 3 – to accommodate interim results for the benefit of the treatment, adjust statistical analysis, or to reach early termination of an unsuccessful design, a process called an "adaptive design".

Adaptive designs within ongoing Phase 2–3 clinical trials on candidate therapeutics may shorten trial durations and use fewer subjects, possibly expediting decisions for early termination or success, and coordinating design changes for a specific trial across its international locations.

According to FDA approximately 25-30% of drugs move to the next phase.

Summary

- Phase 3 involves testing in 100s – 1000s patients with the disease at multiple centers around the world.

- Well-controlled, comparative trials designed to confirm the safety and efficacy of the drug within the therapeutic dose range
- Aim to use conditions similar to those in which the drug would be used if approved for marketing
- Involves thousands of patients to create an adequate database to assess the safety profile and efficacy and to enable accurate drug labelling
- Obtain all the pertinent data that regulatory agencies will need to evaluate the drug

Once a Phase III study has positive results New Drug Application (NDA) files can be submitted to responsible regulatory authority to get permission to market the medicine.

Phase 4 trials – Post Approval Studies

A Phase 4 trial is also known as a Post-marketing Surveillance trial or drug monitoring trial to assure long-term safety and effectiveness of the drug, vaccine, device, or diagnostic test. Phase 4 trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives regulatory approval to be sold. Phase 4 studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or to position the medicine on an appropriate way. These safety surveillance studies are designed to detect rare or long-term adverse effects over a much larger patient population and longer time period. In some cases, new endpoints can be added to assess those health outcomes which might not detected during Phase 1 to Phase 3. There are many examples where new side effects discovered (e.g.: rofecoxib (Vioxx) a COX-2 selective non-steroid anti-inflammatory drug) voluntarily withdrew from the market because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use which proves the importance of Phase 4 trials.

Summary:

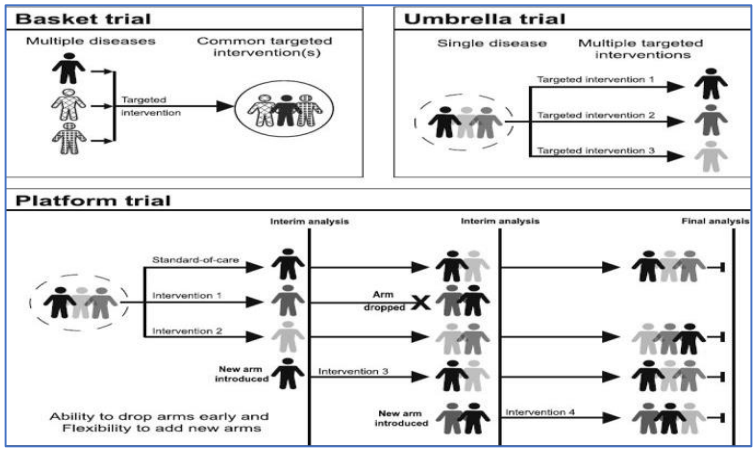
- Several thousand volunteers who have the disease/condition
- Performed after drug approval and related to the approved indication
- Post-marketing studies to answer questions such as:

- Where and how do we position the products?
- How much do we charge?
- How do we promote and differentiate?
- What about the competition?
- Long-term risk and benefits
- Mortality / morbidity studies
- Epidemiological studies
- Studies in new regions
- Assessment of novel health outcomes (endpoints)

Complex Clinical Trials

Answering to the challenges set by Regulatory Authorities and the fast-changing environment in 21st Century, new study designs were introduced.

1. **Basket trials,** where multiple disease subjects enrolled with common targeted intervention(s).
2. **Umbrella trials**, where a single disease is under investigation with multiple targeted intervention(s).
3. **Platform trials**, where the trial design gives the possibility to drop treatment arms early with the flexibility to add new arms any time.



3. FIGURE, COMPLEX CLINICAL TRIALS, IMAGE CREDIT: PARK ET AL. TRIALS (2019) 20:572

III. Effect of Clinical Studies on Society

Economical

In addition to contributing to the accomplishment of strategic and growth objectives in the economy, clinical trials also help generate substantial income in countries where such trials are performed. It is a generally accepted macroeconomic proposition that the generation of one unit of income also increases the fiscal revenue. Methodology experts engaged in planning fiscal revenues calculate the fiscal result of the new revenues at a tax and revenue ratio of 40% at macroeconomic level. Accordingly, it is relatively easy to calculate the fiscal revenues depending on where the incomes are generated during clinical trials (at health institutions, doctors or the CROs). Of course, if a larger part of the income is absorbed by private individuals, the fiscal revenue may be even higher. The types of the fiscal revenues may be as follows:

- In the case of institutions (health, CRO)
- Corporate Income Tax
- Value Added Tax
- Local business taxes
- In the case of healthcare professionals
- Personal Income Tax
- Social security contributions and taxes
- Employee contributions

Fiscal experts also consider the secondary or indirect impacts of the income earned by private individuals, because a sizable proportion of such income is spent on consumption, generating thereby massive amounts of VAT revenues. Employment generated by clinical trials is another important macroeconomic effect. In addition to generating employment, clinical trials also entail a substantial tax capacity since highly qualified individuals – with language skills and being also competitive in international labor market – employed in clinical trials, earn incomes many times higher than the level of the average income in the national economy concerned.

It is an important task to ensure that experts and managers involved in the planning and realization of the budget are fully aware of the fact that the entirety of the clinical trials represents already now a massive tax capacity and subject to applying favorable/investor-friendly tools the potentially increasing volume of clinical trials will generate additional tax revenues for the budget. At present the fiscal policy has not yet fully perceived the macroeconomic importance and significance of the complex clinical trials. Clinical trials mobilize a significant economic potential each year.

The entities organizing and performing the trials (CRO, Pharmaceutical Companies) realize additional spending. Of these the most important items are as follows: – employee wages and contributions – operation of the infrastructure (office, IT, etc.) – transport, legal activity – approval fees, etc.

Health

Patients' life expectancy has improved considerably as a result of pharmaceutical innovation in the recent decades. In the case of certain seemingly incurable diseases (AIDS, lymphoma etc.) the new treatments now prolong the life of the patients sometimes by decades. Breakthroughs have been achieved in the case of countless chronic illnesses for the benefit of millions of patients, whose quality of life improved immensely. Owing to shortages in financing, the possibilities of Eastern European countries with regard to healthcare are way behind those of Western European countries or the US, thus clinical trials enable free access to the sometimes-expensive therapies. Thousands of patients are given a chance year after year to access innovative therapies that would be beyond their reach without clinical trials. Of course, in addition to the health benefits for the patients, clinical trials save money billions for the Health Insurance Funds each year. The health institutions, the health service system and doctors enjoy further benefits by joining a global information network they would have no access to without clinical trials. Participation in clinical trials results in significant improvements in doctors' expertise and qualification standards. Access to the R&D achievements in the given therapeutic area offers them both short- and long-term opportunities. Meanwhile, the respective doctors' research methodological, data processing,

statistical and IT skills also improve. Accordingly, doctors participating in clinical trials become increasingly well versed in the latest knowledge, benefiting both patients and the health "system as a whole". The publication of the results of clinical trials in international periodicals adds much to the scientific performance of the given country's clinical doctors and raises the value of their performance significantly. Another especially important aspect of clinical trials is the possibility for participating doctors to earn considerable supplementary income.

Scientific

The pharmaceutical innovation adds much more to the science than just a medicine. As it was already expressed developing medicines is a joint venture of different scientific areas where the innovation complements each other such as Medicine Design, BioMedicine Design, Small Molecule, Biotherapeutics Product. The strictly regulated drug Research and Development course give space to those areas which can supplement the core such as Process Development, Simulation and Modeling Science, and Clinical Trial Supply.

Precision Medicine relies on the use of biological indicators called biomarkers to classify patients by their risk for certain diseases and/or response to treatment and to precisely characterize their genotype, or genetic code, and phenotype, or physical traits. The emergence of next-generation DNA sequencing technologies has revolutionized the use of human genetics for pharmaceutical R&D by providing the ability to conduct a deeper analysis of genotype in the context of detailed phenotypes. This has generated unprecedented insight into the genetics of human disease and a wealth of novel drug targets and biomarkers.

Phenotyping technologies allow better understanding of human physiology and disease in unprecedented detail, for identifying and validating better biomarkers and response to treatment. These include high throughput omics technologies (e.g., transcriptomics, proteomics, metabolomics), microbiome profiling, flow cytometry, and electronic biomarkers such as actigraphy (i.e., the measurement of patient movement in real time using mobile sensors). Digital biomarkers are gaining increasing importance as an approach to defining more precise outcome measures and clinical research endpoints. These can include, for example, cognitive tests in the form of games on tablets, mood, and disease progression by

voice recording, and actigraphy, among other measures. Health information technology platforms refer to systems that help collect, store, and analyze vast amounts of health data with a particular focus on correlating phenotypic and genotypic information (sometimes referred to as “big data”), which are becoming more readily available to the research community. Though many people first became aware of mRNA technology because of COVID-19 vaccines, it is not new to the scientific community. For decades, scientists have studied mRNA, looking for ways to unlock its potential to prevent and treat disease. While the mechanism of action for mRNA technology is relatively simple—once inside cells, it instructs them to build proteins—researchers have had to work for years develop technologies to allow mRNA to work in the real world. mRNA has proved to be a great platform for vaccine development (and potentially therapeutics), so that our own cells can do the demanding work of producing proteins, resulting in an immune response which helps protect us against diseases. The next wave of mRNA scientific innovation is expanding in the infectious disease arena with development programs in influenza and shingles, also exploring its versatility in the areas of rare genetic diseases or even in oncology.

IV. Common challenges in Clinical Trials

New ways to deliver Clinical Trials earlier

“Speed up” approach

Reducing cycle time in clinical trials is crucial for accelerating the development of new treatments and bringing them to patients faster. Here are several strategies to help streamline and expedite the clinical trial process:

Efficient Protocol Design

Develop a well-designed protocol that focuses on the essential endpoints while minimizing unnecessary procedures and data collection. A streamlined protocol can reduce the time required for study conduct and data analysis.
Feasibility Assessment: Conduct thorough feasibility assessments to identify potential challenges and bottlenecks early on. Evaluate factors such as patient population availability, site capacity, and recruitment strategies to ensure realistic timelines.

Site Selection and Activation

Choose sites with experience and capacity for timely enrollment. Implement efficient site activation processes, including protocol training, document collection, and regulatory approvals. Effective communication and collaboration with sites are crucial for minimizing delays.

Patient Recruitment and Retention

Deploy initiative-taking recruitment strategies, such as leveraging digital marketing and social media, engaging patient advocacy groups, and using patient databases. Implement retention strategies to enhance patient engagement and minimize dropout rates.

Streamlined Data Collection

Utilize electronic data capture (EDC) systems to streamline data collection, validation, and monitoring processes. EDC reduces the need for manual data entry, enhances data quality, and facilitates real-time data access for analysis.

Risk-Based Monitoring (RBM)

Implement RBM approaches to focus monitoring efforts on critical data and high-risk areas. This allows for more efficient use of resources and reduces the time and cost associated with on-site monitoring visits.

Centralized Institutional Review Board (IRB) Review

Consider using centralized or independent IRBs to expedite the review and approval process. These entities can provide faster and more consistent reviews across multiple sites.

Parallel Processes

Identify activities that can be conducted concurrently instead of sequentially. For example, start preparing regulatory submissions while the protocol is being finalized, or initiate site training while the contract negotiations are underway.

Adaptive Trial Design

Consider adaptive trial designs that allow for modifications during the study based on accumulating data. Adaptive designs enable early decision-making, such as adjusting sample size, treatment arms, or endpoints, which can significantly reduce trial duration.

Collaboration and Technology

Foster collaboration among stakeholders, including investigators, sponsors, contract research organizations (CROs), and regulatory authorities. Utilize technology solutions, such as electronic Trial Master Files (eTMFs), e-signatures, and real-time collaboration platforms, to streamline document management and facilitate efficient communication.

Regulatory Expertise

Engage regulatory experts early in the trial planning process to ensure compliance with regulatory requirements. Proactive engagement and clear communication with regulatory agencies can help expedite regulatory submissions and approvals.

Continuous Process Improvement

Continuously evaluate the trial process and identify opportunities for improvement. Analyze performance metrics, capture lessons learned, and implement changes in subsequent trials to optimize efficiency.

It is important to note that while speeding up clinical trial timelines is desirable, maintaining patient safety and data integrity should always be the top priority. Balancing speed with quality is crucial to ensure reliable results and the well-being of trial participants.

Decentralized Clinical Trials

The Decentralized Clinical Trials (DCT) is an interesting leading-edge approach to further develop the execution of clinical studies.

Decentralized Clinical Trials represent a spectrum of alternatives for how, when, and where patients can participate in a clinical trial – ranging from a single digital interaction to never coming to a research site.

Individual study components can be decentralized, to provide flexibility in the protocol design ranging from hybridized decentralized trials to in some case fully decentralized trials.

Vision is to create a more patient centric clinical trial by introducing trial elements that allow patients to participate in a more flexible way. Impact is to decrease burden of participation on patients increasing recruitment, enrollment, retention, & adherence ultimately reducing costs and cycle times.

These are the following possibilities which can either or all be utilized during the execution of clinical trials:

1. Remote Informed Consent
2. eConsent
3. Sensors and Wearables
4. Decentralized Sites (so called mobile units)
5. Flexible Sample Collection
6. TeleHealth
7. eCOA/ePRO
8. Home Health
9. Direct to Patient Drug Delivery

Although there are some „compatibilities" not all clinical trials can be conducted in this setting.

Studies with High Compatibility for DCT:

- Oral treatment

- Topical treatment
- Subcutaneous treatment
- IV administration, as permitted in study protocol, e.g., with Remote Clinical Trial Visit Provider Participant Exclusion:
    - If participant resides in a different country than the PI
    - Shipping to a patient location other than home (e.g., hotel or business)

Studies with Low Compatibility:

- Phase 1 – First in Human
- IMP with short expiry/stability (temperature complexity)
- Third Party Blind studies
- Controlled Substance
- Products that require sterile preparation
- Hazardous products that require special preparation or handling
- Products that require a medical professional administration unless a Remote clinical Trial Visit professional is provided)
- Products that require extra-ordinary storage conditions
- IV infusion pumps (varies depending on the protocol and if a Remote Clinical Trial Visit can be provided)

Studies that will require additional planning for DtP delivery options:

- Studies with a lot of titrations (dosage can go up and down pending on lab values)
- Toxic/radioactive drugs (transportation laws may not allow)
- Studies that fall under a REMS (Risk Evaluation and Mitigation Strategy) categorization per regulatory
- Studies should not be shipping IMP across State lines
- IMP that requires storage from 2-8C or frozen

During a Decentralized Clinical Trials, the following elements can be used:

- eCOA: eCOA is the collection of Clinical Outcome Assessments (COA) data in a clinical trial via technology. There are four types of Clinical Outcome Assessments.
    - Patient-reported outcomes (PROs)
    - Clinician-reported outcomes (ClinROs)
    - Observer-reported outcomes (ObsROs)
    - Performance outcomes (PerfOs)

Electronic Clinical Outcome Assessments (eCOA) measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions. eCOA includes Electronic Patient Reported Outcomes (ePRO), Performance Outcomes (PerfO), Clinician Reported Outcomes (ClinRO) and Observer Reported Outcomes (ObsRO). The ePRO/eCOA solution offers accurate reporting for unparalleled assessments directly from the patient.

What are the benefits? The ePRO/eCOA solution provides clean data in real-time and improves participant retention and engagement. Clinical study members have unprecedented access to critical efficacy and safety data. This includes administrative reports via specialized web portals and may consist of compliance data and safety alerts against preset levels. ePRO/eCOA also supports compliance for both FDA 21-CFR Part 11 and ICH GCP, which helps with the overall data quality.

eConsent

eConsent is a technology that enables the participant to receive information from the paper Informed Consent Document (ICD) into a digital format and execute the consenting process. Remote Informed Consent enables informed consent to be performed remotely between a participant's home and study site. eConsent is the transformation of the traditional paper-based informed consent process to a digital format that enables use of printed text, voiceover narratives, multimedia components and knowledge checks to facilitate enhanced participant comprehension.

- The use of an eConsent system is intended to enhance the participant's experience and improve their comprehension of the ICD using multi-media educational components, where allowable and implemented by the study team.
- The system is also used as a tool to further facilitate discussions between the participant and the Investigator (or delegated site staff) during the informed consent process.

Flexible/Alternative Sample Collection

Flexible sample collection refers to any sample collection done outside the site location; analyzed in accordance with the requirements of the protocol and data management plan. This includes sample collection during a Remote Clinical Trial Visit, participant self-collection at home, or the use of local labs for any blood draws. Depending on the method of flexible sample collection, other processes around certification, instructions, training, data collection and data transfer must be followed. Provides participants with necessary tools & info they need to collect various sample types at home (nasal swab, stool samples, blood, etc.) & send the sample back to site or central lab to be analyzed.

Examples:

- Mobile phlebotomy / home health visit (most common)
- Participant self-test at home (e.g., Tasso at-home samples collection device currently in use in Phase 1 validation study for PK or Covid-19 studies)

Depending on the sample type, the method by which the sample is sent back to the site or central lab could be by mail-drop off or courier pick up at participants home.

Remote Clinical Trial Visits (RCTVs)

Clinical trial visits that are performed by a qualified health care professional (HCP) in the participant's home or other location, under the oversight of the Principal Investigator (PI).

May include physiological observation, IMP administration, sample collection, education, and support. Providing services in the participants home or other location lessons the burden on the participant and site.

Sensors, Wearable & Mobile Applications (apps)

Portable sensors and wearables that include hardware and software (including mobile apps) that support data collection, measurement, storage, and transmission from a variety of sources, including study participants themselves. This can include tools that automatically collect and transmit continuous data, as well as tools that allow for data collection in real time or at specific points in time.

An increasing number of clinical trials are being designed in which mobile technology—including smart phone applications, sensors, wearables, ingestible, implantable, and other mobile platforms containing sensors—are being used to capture data of interest to clinical trial stakeholders and participants. These technologies can be used to develop novel endpoints.

There are many potential benefits to incorporating a sensor-based technologies into clinical studies. These benefits include but are not limited to:

- Detection and tracking of disease symptoms
- Stratification of populations for trial engagement
- Wellness management, patient engagement
- Monitoring of vital signs
- Identification of novel biomarkers and digital endpoints

Telehealth is direct audiovisual connection between an investigator or study staff and a remotely located participant using synchronous audio and/or video telecommunications technology. May include the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research, and evaluation, and for the continuing education of health care providers. Telehealth may also be referred to as "telemedicine”.

It should be mentioned may not all DCT elements can be used due legislations and regulations differences in the country where a clinical study is planned to be executed. Before utilizing the elements, it must be investigated if the Country laws and regulations permits.

Direct to Patient Drug/IMP Delivery (DtP)

Allows for Investigational Medical Product (IMP)/ comparator delivered to a Trial participant to their home or pre-approved location and in compliance with local regulatory requirements.

Current Strategies of DtP may include:

1, Site to Patient

Direct shipment of clinical supplies and Investigational Medical Products (IMP) to the participant's residence or other agreed upon location (e.g., participant's work).

2, Central Pharmacy to Patient

A Central Pharmacy or Local Pharmacy is different than a Distribution Depot, as a Central or Local Pharmacy has a licensed pharmacist. The licensed pharmacist is licensed in the state, region and/or Country the IMP is being shipped from. This enables IMP to be sent to a participant from the Central /Local Pharmacy based on a prescription from the Principal Investigator.

3, Alternative Sites (Mobile Sites & Virtual Sites)

Meet the participants closer to where they are using mobile, virtual, or remote clinical sites.

4, Extend trial delivery beyond the reach of a traditional site

Allow studies flexibility in where patients are seen (i.e., geographic location and visit setting)
Allow study teams to target specific geographics or patient populations more easily.

Digitalize clinical trials

Digitalizing clinical studies can bring numerous benefits, such as improved efficiency, data accuracy, participant recruitment, and overall study management. Here are some options for digitalizing clinical studies.

Electronic Data Capture (EDC)

Replace paper-based case report forms with electronic data capture systems. EDC platforms allow researchers to collect, manage, and analyze study data digitally, eliminating the need for manual data entry and reducing errors. Some popular EDC systems include Medidata Rave, OpenClinica, and REDCap.

Wearable Devices and Sensors

Use wearable devices and sensors to collect real-time data from study participants. These devices can monitor vital signs, activity levels, sleep patterns, and other relevant health metrics. Examples include smartwatches, activity trackers, and biosensors. Integrating wearable technology with study protocols can provide continuous and objective data, reducing reliance on self-reporting.

Mobile Health (mHealth) Apps

Develop mobile applications that enable participants to report outcomes, track symptoms, adhere to study protocols, and receive study-related information. mHealth apps can also serve as reminders for medication adherence and data collection. These apps can be integrated with other technologies like wearable devices for seamless data transmission.

Telemedicine and Remote Monitoring

Incorporate telemedicine solutions to conduct virtual visits, reducing the need for in-person visits and enhancing remote participation. Remote monitoring tools can be used to collect data from participants in their own environments, allowing for more comprehensive and accurate information. This approach is particularly useful for long-term studies or patients with limited mobility.

Cloud Computing and Data Analytics

Utilize cloud-based platforms for secure storage, sharing, and analysis of study data. Cloud computing allows for centralized data management, collaboration among researchers, and scalability. Advanced analytics tools can help process large datasets, identify patterns, and derive meaningful insights, facilitating faster and more accurate decision-making.

Blockchain Technology

Explore the use of blockchain to enhance data security, integrity, and transparency in clinical studies. Blockchain can provide a decentralized and tamper-proof system for managing informed consent, data sharing, and audit trails. It can also facilitate secure patient identification and streamline data exchange between stakeholders.

Artificial Intelligence (AI) and Machine Learning (ML)

Leverage AI and ML algorithms to analyze complex datasets, identify correlations, predict outcomes, and support decision-making in clinical studies. These technologies can aid in participant selection, adverse event detection, protocol optimization, and personalized medicine approaches.

Virtual Reality (VR) and Augmented Reality (AR)

Use VR and AR technologies to create immersive training environments for study personnel, simulate patient scenarios, and enhance patient education and engagement. These technologies can improve training efficiency and provide more realistic experiences without the need for physical resources.

It is important to note that implementing digital technologies in clinical studies requires careful consideration of data privacy, security, regulatory compliance, and participant acceptance. Collaboration with relevant stakeholders, including researchers, sponsors, ethics committees, and regulatory authorities, is essential for successful digital transformation in clinical research.

Artificial intelligence

The use of artificial intelligence will be inevitable during the course of the clinical trials although it would need careful consideration before utilization AI based technology. There are some areas where AI seems promising:

1, Improvement in Clinical Trials Efficiency for Treatment Development

AI-powered software, such as ClinicalTrial.ai, uses natural language processing and review to streamline the metadata management process, provide guidance to clinical research sites, and offer analytics to optimize study execution and save time.

2, Facilitating Quality Control and Compliance in Clinical Trials

AI-powered software can optimize data collection, automate reminders for protocol-driven activities, and alert research staff of any departures from normal operations, helping to reduce protocol violations.

3, Adaptive Clinical Trials

AI-powered software can help reduce the length of clinical trials by allowing researchers to quickly adjust the study protocol in response to changes in the efficacy and safety of treatments.

4, Identifying Eligible Patients for Clinical Trials

AI technology can help identify, with precision, millions of patients who could be eligible to participate in a clinical trial.

5, Simulation and Modeling in Clinical Trials

AI-enabled systems can help simulate a variety of factors that may affect a study, such as recruitment rate or attrition. This capability can help researchers efficiently allocate resources, predictions of patient outcomes, and more.

6, Automate Medical Image Evaluation

AI-enabled systems can be used to automate medical image evaluation to detect and classify targets accurately. This is particularly useful when assessing the effectiveness of treatments for conditions, like cancer, characterized by a variety of visible symptoms and biomarkers.

7, Clinical Decision Support

AI-driven systems can provide clinicians with automated guidance in the diagnosis and treatment of diseases, such as determining the best treatments, prognoses, and other clinical decision-making.

8, Adverse Event Detection in EMR Systems

AI-powered systems are used to monitor Electronic Medical Records (EMRs) for signs of adverse drug events and medical errors in order to alert healthcare providers in real-time.

9, Personalized Medicine

AI-powered software can be used to identify rare genomic or epigenomic markers, which can help develop treatments tailored to an individual's unique biology.

10, Automated Outcome Prediction and Benchmarking

AI can provide predictive analytics to help clinicians judge how well a given patient will respond to a given treatment, or automatically compare health standards and outcomes to clinical benchmarks.

Compliance with Rules and Regulations

Compliance with rules and regulations is essential in conducting clinical trials to ensure the safety of participants, the reliability of data, and the ethical conduct of research. Here are some key aspects of compliance in clinical trials:

Regulatory Authorities

Clinical trials are regulated by governmental bodies such as the Food and Drug Administration (FDA) in the United States, the European Medicines Agency (EMA) in Europe, and other similar agencies worldwide. Compliance requires adherence to their guidelines, including proper documentation, reporting, and ethical considerations.

Institutional Review Boards (IRBs) and Ethics Committees (ECs)

These independent bodies review and approve the initiation and conduct of clinical trials to protect the rights and welfare of human subjects. Compliance involves obtaining their approval before starting a trial and providing them with ongoing updates.

Informed Consent

Participants in clinical trials must provide informed consent, understanding the study's purpose, procedures, potential risks, benefits, and their rights as participants. Compliance requires obtaining written informed consent from participants or their legally authorized representatives.

Good Clinical Practice (GCP)

GCP is an international ethical and scientific standard for designing, conducting, monitoring, recording, analyzing, and reporting clinical trials. Compliance with GCP guidelines ensures the integrity of trial data, participant safety, and overall trial quality.

Protocol Compliance

The clinical trial protocol outlines the study objectives, design, methodology, and participant eligibility criteria. Compliance involves strictly following the protocol throughout the trial, including administering investigational products, conducting assessments, and collecting data as specified.

Safety Reporting

Compliance requires timely reporting of adverse events (AEs) and serious adverse events (SAEs) occurring during the trial to regulatory authorities, IRBs/ECs, and sponsors. Proper documentation, assessment, and reporting of AEs/SAEs are crucial for participant safety monitoring.

Data Integrity and Recordkeeping

Compliance necessitates maintaining accurate, complete, and reliable records of all trial-related activities, including data collection, analysis, and storage. Data integrity is vital for regulatory submissions, audits, and inspections.

Monitoring and Auditing

Compliance involves regular monitoring of the trial by sponsors or contract research organizations (CROs) to ensure protocol adherence, data quality, and participant safety. Regulatory authorities may also conduct inspections or audits to verify compliance.

Investigational Product Handling

Compliance includes proper storage, dispensing, administration, and accountability of investigational products (e.g., drugs, devices) used in the trial, following applicable regulations and sponsor-specific procedures.

Reporting and Registration

Compliance requires the timely submission of trial results, whether positive, negative, or inconclusive, to regulatory authorities, trial registries, and scientific journals, promoting transparency and avoiding publication bias.

It is essential for researchers, sponsors, investigators, and all involved parties to be knowledgeable about the relevant rules and regulations governing clinical trials in their respective jurisdictions to ensure compliance and maintain the highest standards of ethical conduct and patient safety.

Managing Multiple Sites

In clinical research and development, it is common to conduct multinational studies involving 10-20 Countries, 200-300 Investigational Sites and over 3000 Participants. Sometimes these studies are short term but due to the nature of the disease under study it can be long-lasting as 2-5 years. This is tremendous amount of job and working hours in a matrix structure environment. Managing multiple sites in clinical trials therefore extraordinarily complex, but proper planning, coordination, and communication can help ensure smooth operations and data integrity across all sites. Here are some key considerations for managing multiple sites in clinical trials:

Site Selection

Choosing sites based on their expertise, infrastructure, patient population, and ability to meet the study requirements. Consider factors such as the availability of qualified investigators, access to necessary resources, and the potential for patient recruitment. Finding the proper sites at first time under limited time is essential.

Site Initiation

Conduct thorough site initiation visits to provide training on the study protocol, procedures, and regulatory requirements. Establish clear lines of communication and ensure that all site staff are aware of their roles and Responsibilities.

Protocol Standardization

Standardize procedures across sites to ensure consistency in data collection and reduce variability. Develop detailed standard operating procedures (SOPs) that clearly outline each step of the trial and provide training to site staff to ensure adherence to the protocol.

Project Management

Assign a project manager more precisely a project management team (consist of clinicians, start-up managers, global and local project managers) who will be responsible for overseeing the trial at all sites. The project manager should maintain regular communication with country staff to provide ongoing support and address any issues or concerns that may arise.

Training and Education

Provide comprehensive training to site staff on all aspects of the study, including the protocol, data collection procedures, adverse event reporting, and regulatory compliance. Regularly update sites on any protocol amendments or changes to ensure consistent implementation across all sites.

Communication and Collaboration

Establish effective communication channels between the central study team and the individual site staff. Conduct regular meetings, either in-person or remotely, to address questions, share updates, and discuss challenges. Foster a collaborative environment that encourages open communication and the sharing of best practices among sites.

Monitoring and Quality Assurance

Implement a robust monitoring plan to ensure that each site is conducting the trial in compliance with the protocol, regulatory requirements, and good clinical practice (GCP) guidelines. Regularly monitor data quality, source documentation, and adherence to protocol procedures. Consider on-site monitoring visits and remote monitoring strategies as appropriate. Quality Assurance plan is also a key element from the early phase of the study planning because without quality the trial integrity may be jeopardized. Implementation of proper quality assurance Regulatory Authority findings can be minimized.

Data Management

Implement a centralized data management system that allows for secure and efficient data collection, storage, and analysis across multiple sites. Ensure that data management procedures are standardized and establish data verification and quality control processes.

Adverse Event Reporting

Provide clear guidelines and procedures for adverse event reporting at each site. Ensure that site staff promptly report any adverse events or serious adverse events and that they are documented, assessed, and reported in compliance with regulatory requirements.

Regulatory Compliance

Maintain ongoing oversight of regulatory compliance at each site, including adherence to ethical considerations, informed consent procedures, and timely submission of regulatory documents. Regularly communicate with regulatory authorities to address any queries or requests for information.

Site Closeout

Develop a comprehensive site closeout plan to ensure proper documentation, final data collection, return of study materials, and resolution of any outstanding issues. Conduct site closeout visits or remote assessments to confirm that all necessary activities have been completed.

By following these considerations, you can enhance the efficiency, quality, and consistency of data collection and management across multiple sites in clinical trials. Effective management and coordination will contribute to the overall success of the trial while ensuring patient safety and data integrity.

The „Educated Patient and Relatives”

The information and data are widely available on the internet and easy to access. The problem is with this data is that not always adequate, clear, and accurate. Some language is more scientific than an “average” person can understand. Even if someone understand it the lack of background knowledge can lead to misinterpret the complexity and well-regulated environment of clinical trials. There are some elements and possibilities worth the time to walk around this topic.

Educating patients about clinical trials is crucial to ensure their understanding, informed decision-making, and active participation. Here are some common issues related to patient education in clinical trials and strategies to address them:

Lack of Awareness

Many patients may be unaware of the availability of clinical trials or may not fully understand their purpose and benefits. Strategies to address this may include:

1, Public awareness campaigns

Conduct educational initiatives to raise awareness about clinical trials through various channels, including healthcare providers, community organizations, online platforms, and media outlets.

2, Patient advocacy groups/Patient Organizations

Collaborate with patient advocacy organizations to disseminate information about clinical trials and their importance.

3, Physician engagement

Encourage healthcare providers to discuss clinical trial options with their patients and provide information about ongoing trials that might be relevant to their medical conditions.

4, Limited Access to Information

Patients may struggle to access comprehensive and understandable information about clinical trials. Strategies to improve access include:

a, Patient-friendly materials

Develop patient-centered educational materials that explain the purpose of clinical trials, the study process, potential risks and benefits, and the rights of participants. Make these materials available in multiple formats, such as brochures, videos, and websites.

b, Dedicated websites, and registries

Maintain user-friendly websites and clinical trial registries that provide up-to-date information about ongoing trials, eligibility criteria, and contact details for further inquiries.

c, Patient navigation services

Establish patient navigation services to help individuals navigate the clinical trial landscape, answer their questions, and provide guidance on finding appropriate trials.

Complex Study Information

Clinical trial documents and informed consent forms can be complex and contain technical terminology that may be difficult for patients to understand. Strategies to address this include:

Plain language summaries

Provide plain language summaries of study protocols and informed consent forms to help patients understand the trial objectives, procedures, risks, and benefits.

Interpreter services

Ensure that interpreter services are available for patients who have language barriers or limited health literacy to facilitate effective communication and understanding. It is also helpful if the patient participating in a clinical study but should be re-located to a foreign country, but the disease condition requires continuous treatment (e.g.: Russian – Ukrainian war, oncology subject).

Patient support groups

Encourage the formation of patient support groups where individuals considering or participating in clinical trials can share their experiences, ask questions, and receive support.

Fear and Misconceptions

Patients may have fears and misconceptions about clinical trials, including concerns about safety, experimental treatments, or being treated as "guinea pigs." Strategies to address these issues include:

1, Clear communication

Provide clear and honest information about the trial process, safety measures, and ethical considerations to address patient concerns.

2, Personalized discussions

Engage in personalized discussions with patients, addressing their specific concerns and ensuring that their questions are answered.

3, Testimonial sharing

Share stories of patients who have participated in clinical trials and benefited from them to provide reassurance and dispel myths and misconceptions.

4, Informed Decision-Making

Patients need support in making informed decisions about participating in clinical trials. Strategies to facilitate informed decision-making include:

a, Adequate time

Provide patients with sufficient time to review trial information, consult with their healthcare providers, and discuss the decision with their families.

b, Shared decision-making

Encourage shared decision-making between patients and healthcare providers, ensuring that patients' values, preferences, and concerns are considered.

5, Informed Consent process

Conduct a comprehensive informed consent process, ensuring that patients fully understand the trial's purpose, procedures, potential risks and benefits, and their rights as participants.

By addressing these issues through comprehensive patient education efforts, healthcare providers, researchers, and clinical trial stakeholders can enhance patient understanding, engagement, and participation in clinical trials, ultimately improving the overall quality and impact of clinical research.

Slower Recruitment than Planned

Slow recruitment in clinical trials is a common issue that can have significant implications for the study timeline, budget, and statistical power. Not to mention that every single day counts at the end to deliver lifesaving medication to the population. From the companies' point of view this delay can be easily materialized in money. The following are some effects of slow recruitment in clinical trials:

1, Delayed Study Timeline

Slow recruitment can significantly extend the overall duration of the study. Delays in enrolling an adequate number of participants can push back important milestones, such as the start and completion of study phases, data analysis, and final results.

2, Increased Costs

Prolonged recruitment timelines can lead to increased costs associated with site fees, staff salaries, monitoring, and administrative expenses. The extended duration may also require additional resources for participant retention and maintaining study infrastructure.

3, Statistical Power and Data Quality

Slow recruitment can result in insufficient sample sizes, compromising the statistical power of the study. Inadequate sample sizes may lead to inconclusive results or an increased risk of type II errors (false negatives). Insufficient participant numbers may also impact data quality and limit the generalizability of study findings.

4, Competitive Landscape

In certain therapeutic areas, multiple clinical trials may be competing for the same patient population. Slow recruitment can be exacerbated when there is a limited pool of eligible participants due to high demand or specific patient characteristics required by the study.

5, Safety Concerns

Slow recruitment may delay the evaluation of safety endpoints and adverse events, which can impact the assessment of the intervention's safety profile. Timely identification of potential risks and safety concerns is crucial for participant safety.

6, Ethical Considerations

Slow recruitment can prolong the time participants spend in the control group (if applicable) without receiving the potential benefits of the experimental intervention. This delay may raise ethical concerns, particularly if there are alternative treatments available.

External Factors and Generalizability

External factors, such as changes in medical practice, treatment guidelines, or the availability of competing therapies, can influence recruitment rates. Slow recruitment may affect the generalizability of study results if the enrolled participants differ significantly from the broader target population.

Target population is "hidden"

As it was written before in some studies (rare disease) the appropriate subjects are hard to find however in general studies there is a certain population for some reason are reluctant to clinical research or refuse to be participants. This part is the hardest to manage by the companies as they cannot be in direct contact with the subject population (this might vary country by country due to the different rules and regulations). According to the studies showed that 80% (!) of all delays are coming from the slow recruitment.[18,19]
Strategies to mitigate the effects of slow recruitment include implementing proactive recruitment plans, enhancing patient engagement and education, collaborating with patient advocacy groups, refining eligibility criteria, and optimizing communication with healthcare providers. It is important to regularly assess recruitment strategies and make necessary adjustments to improve enrollment rates and minimize the impact of slow recruitment on the trial. Addition to the expected and planned cost to deliver a new medicine to the market, the following hard facts must be considered which are related to the recruitment and put additional financial burden to a trial:

- 37% of sites under-enroll, and 11% fail to enroll a single patient[18]
- Delays can cost Sponsors between $600,000 and $8 million for each day that a trial delays a product's development and launch[18]
- Screen failure rates are significantly costly for sponsors and the cost (on average) across the industry is roughly $1,200 per failure[18]

Improving clinical trial patient engagement is a critical need for faster recruitment. Increasing patient enrollment can play a leading role in the duration and cost of a trial — but this requires a strategic approach to patient recruitment including education.

V. Investigating exploration

Questions to explore

Clinical Trial Professionals agrees that one of the biggest challenges in common during clinical trial execution is how to reduce the recruitment period during a clinical study. According to my Dissertation, one major element of this complex question is not Sponsor dependent. Despite of the efforts Companies put in clinical trial execution they cannot influence the willingness of Subjects to be a study participant.

According to my theory one major element of this issue is the lack of knowledge of the population on general drug research and development including clinical trials. This lack of knowledge may come either if not all from the following factors:

- lack of background knowledge on drug development
- unreliable sources of information
- lack of trust based on different factors
- myths around drug development
- contradictory information

According to my hypothesis by improving the education about clinical trials more individuals inclined to participate in clinical trials. The hypothesis also assumes there is a correlation between understanding the drug research, including clinical trials the purpose and benefits should increase the willingness to be enrolled.

Methodology

To gain information a questionnaire was developed (Appendix 1). This questionnaire is not validated and not intended for general usage only for the purpose of this PhD thesis. It consists of thirty questions and in Hungarian. The questionnaire was designed to be filled out via

computer or via mobile device and consist of demographic questions, single choice questions, multiple choice questions (with the possibility to enter open ended answers), Likert scale questions and rating scale questions.

The participation was voluntarily and completely anonymous. Based on “dummy run” the questionnaire can be filled out in 10 minutes.

Sample size

It was planned to have in between 50-200 individuals to complete the questionnaires. Its sample size can provide ample data for meaningfully processed considering the desired confidence level, population variability and some margin of errors. The sample size was calculated via on-line sample size calculator assuming the margin of error is either 7% or 5% as shown below.

	Sample size 1	Sample size 2	Sample size 3	Sample size 4
Confidence level	70%	85%	90%	95%
Margin of error	7%	7%	7%	7%
Expected sample size	56	106	139	196

4. Figure, Margin of error set for 7%

If the margin of error set for 5% the following sample size emerging.

	Sample size 1	Sample size 2	Sample size 3	Sample size 4
Confidence level	70%	85%	90%	95%
Margin of error	5%	5%	5%	5%
Expected sample size	109	208	273	385

5. Figure, Margin of error set for 5%

Based on the calculation above a sample size of 200 would give 95% Confidence level with a Margin of Error of 7% or 85% of Confidence level with the Margin of Error of 5%. This might meet the desired statistical constraints set by this PhD thesis.

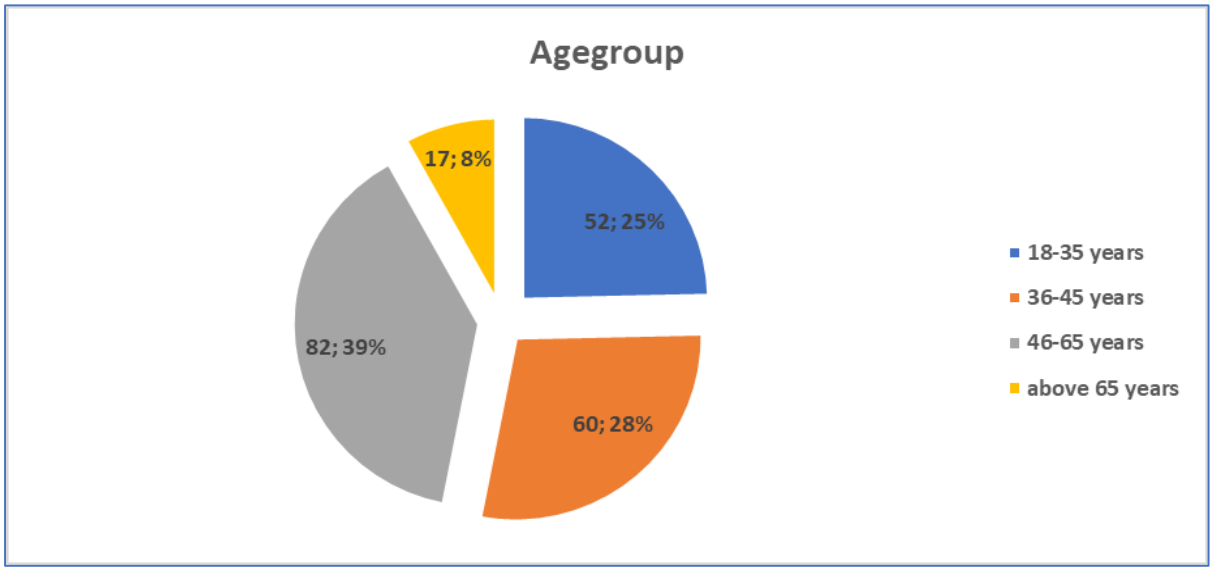
VI. Results

The data collection was started 01st February 2023 and lasted until 18th April 2023. During this time period 211 individual completed the questionnaire which can provide ample data to set the Confidence level to 85% with the Margin of Error of 5%. The average time for filling out the questionnaire was 09:40 minutes.

Basic demography data

Age

A total of 211 individual filled out this question. As it can be seen the age group of 46-65 years are represented the most with their 39%, the 36-45 years age group 28%, 18–35-year group 25% and the above 65 years age group represented.

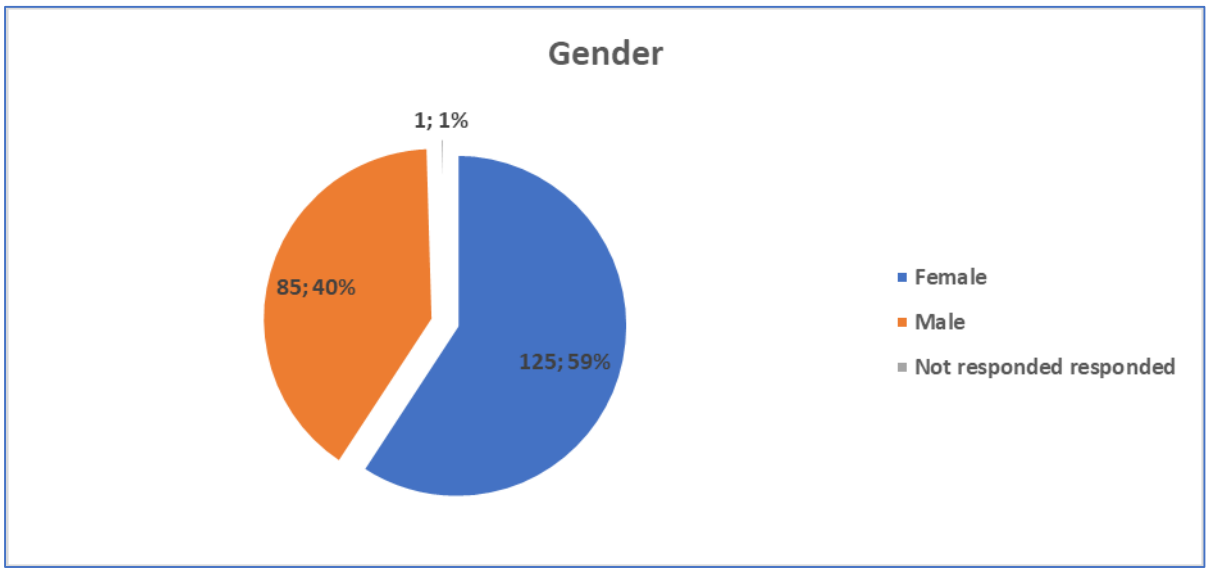


6. FIGURE, AGE GROUP

Gender

The distribution slightly in favor of female participants. 59% (n=125) of participants were female, 40% (n=85) were male. 1 participant did not answer the question. None of the

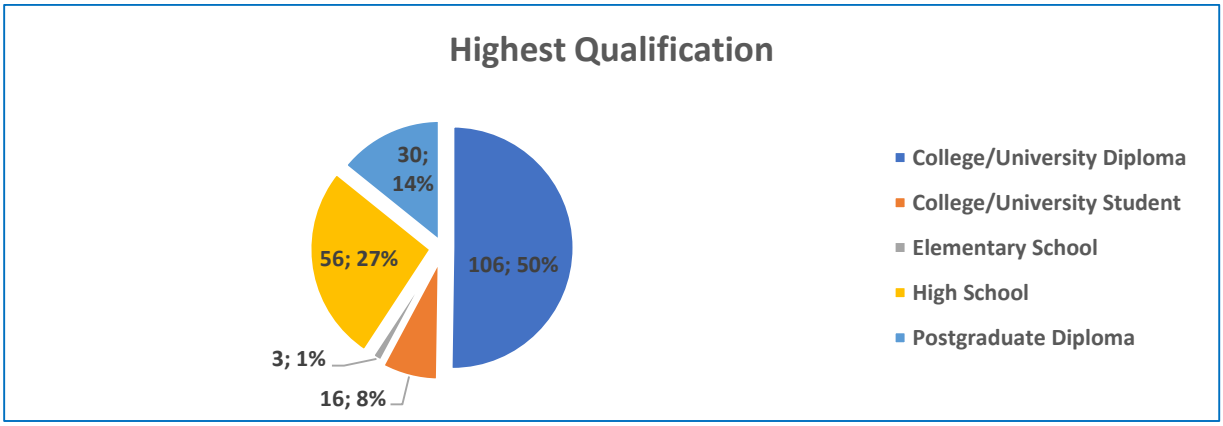
participants marked the possibility of “Other” option. Based on the sample size of both gender group subgroup analysis might be performed.



7. Figure, Gender Group Distribution

Qualification

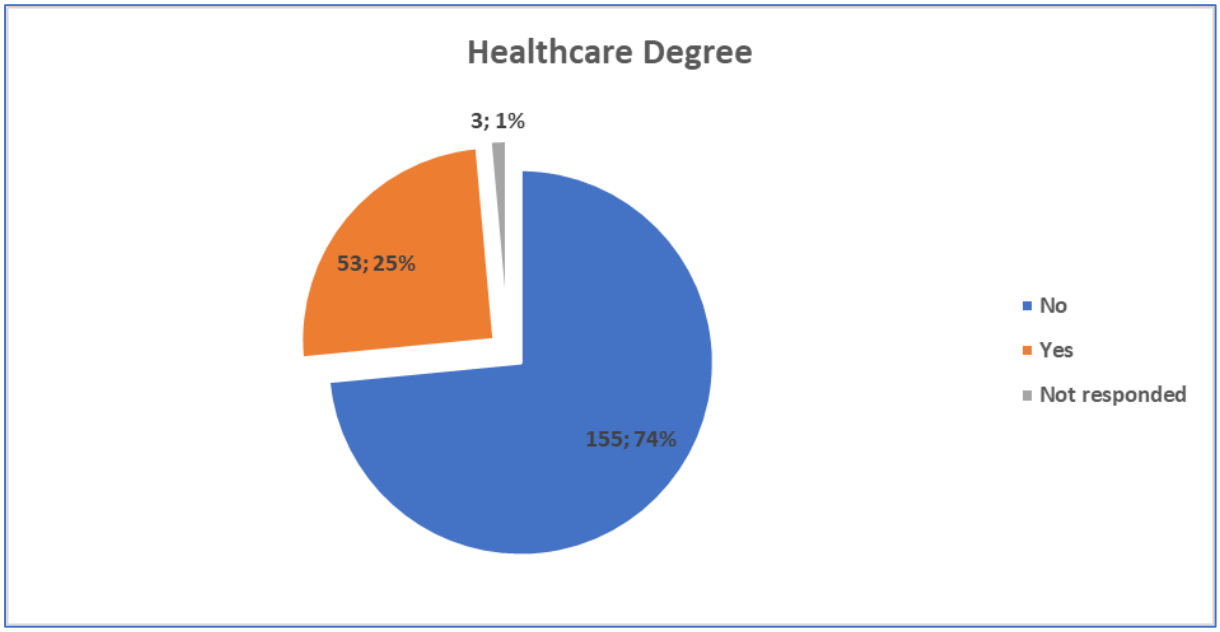
According to the research nearly 50% (n=106) of the participants has either college or university degree with an addition of 14% (n=30) postgraduate diploma. Moreover, an addition of 8% (n=16) is currently participating in higher education. 27% (n=56) indicated the high school diploma as the highest degree of education and 1% (n=3) has elementary school degree.



8. Figure, Distribution Group by Highest Qualification

Healthcare degree

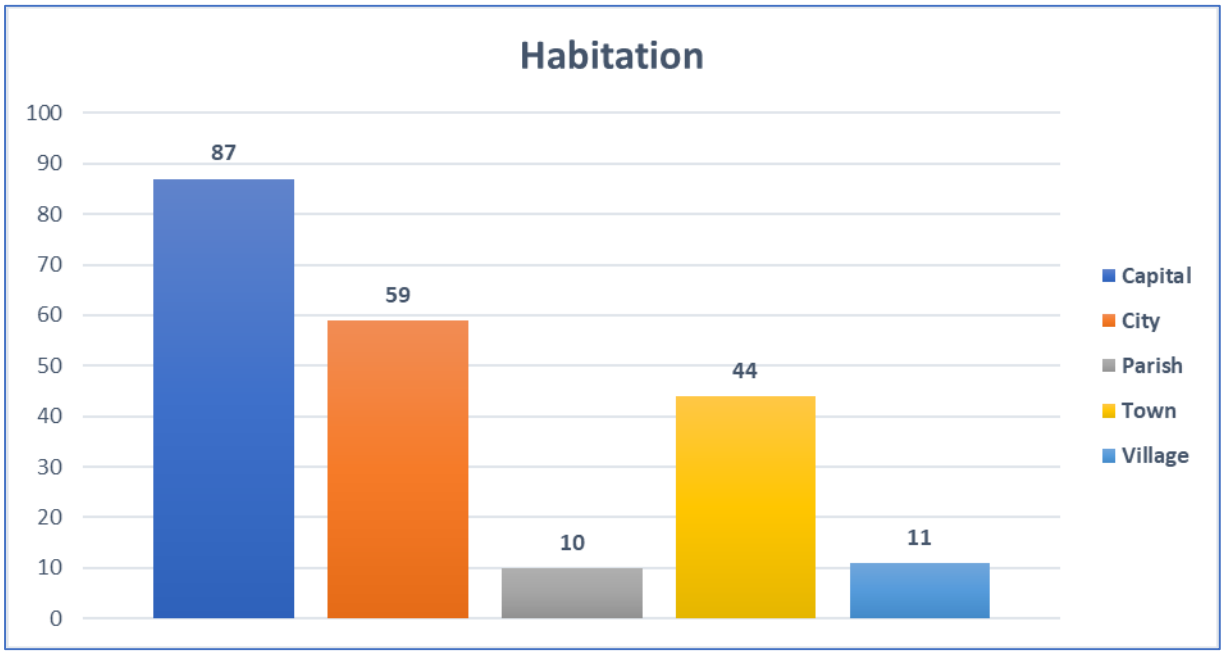
From research perspective I found it important to find out if the participant has healthcare degree or not to split into 2 sub-group to the analysis. Are there differences in between those who holds healthcare degree 25% (n=53) or not 74% (n=155). 1% (n=3) of participants did not answer to this question.



9. FIGURE, HEALTHCARE DEGREE HOLDERS

Habilitation

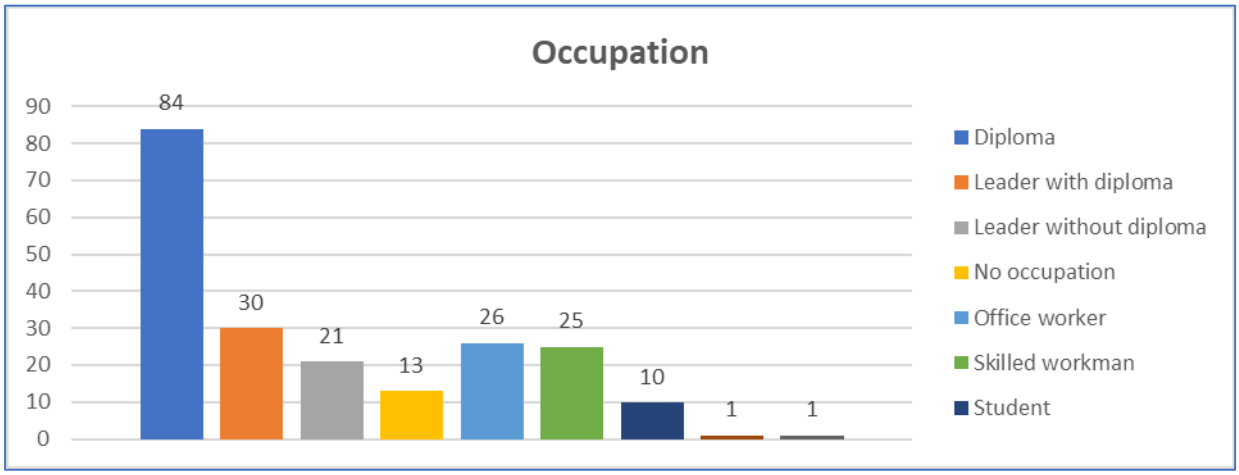
Another possibility to form sub-groups is the habilitation of the participants. 41% (n=87) are living in the capital, 28% (n=59) are living in a city, 21% (n=44) are living in a town, 5-5% (n=11, n=10) of the participants are living in a parish/village setting.



10. Figure, Group Distribution by Habilitation

Occupation

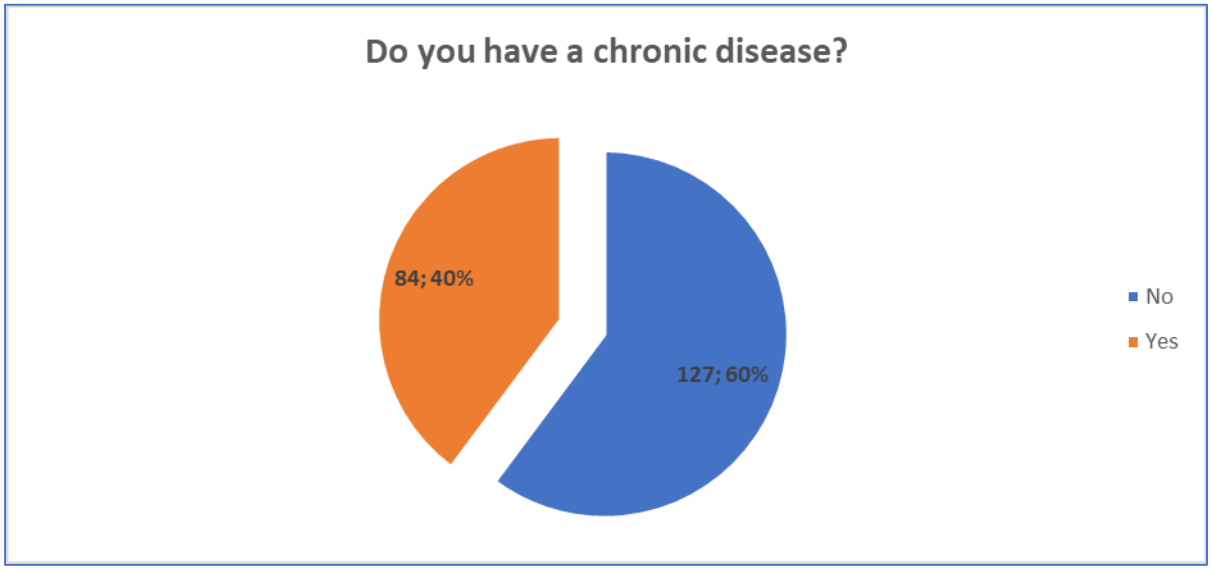
As we can see from the data below, 19% (n=84) have a job required a diploma. 7% (n=30) in a leader position requires a diploma. 5% (n=21) in a leader position which did not requires a diploma. 3% (n=13) reported that no occupation, 6% (n=26) is an office worker, 6% (n=25) is a skilled worker, 2% (n=10) are student. 1 subject reported unskilled worker as an occupation and 1 subject did not answer to the question.



11. Figure, Group Distribution by Habilitation

Chronic disease

60% (n=127) reported no chronic disease and 40% (n=84) reported at least 1 chronic disease. This picture shows, that 40% of the participants has real possibility to participate in Phase II, III and IV clinical trials. They are involved at least 1 chronic disease, therefore during their treatment and clinic visits they have bigger chance to be offered participation in clinical trials involving investigational product.



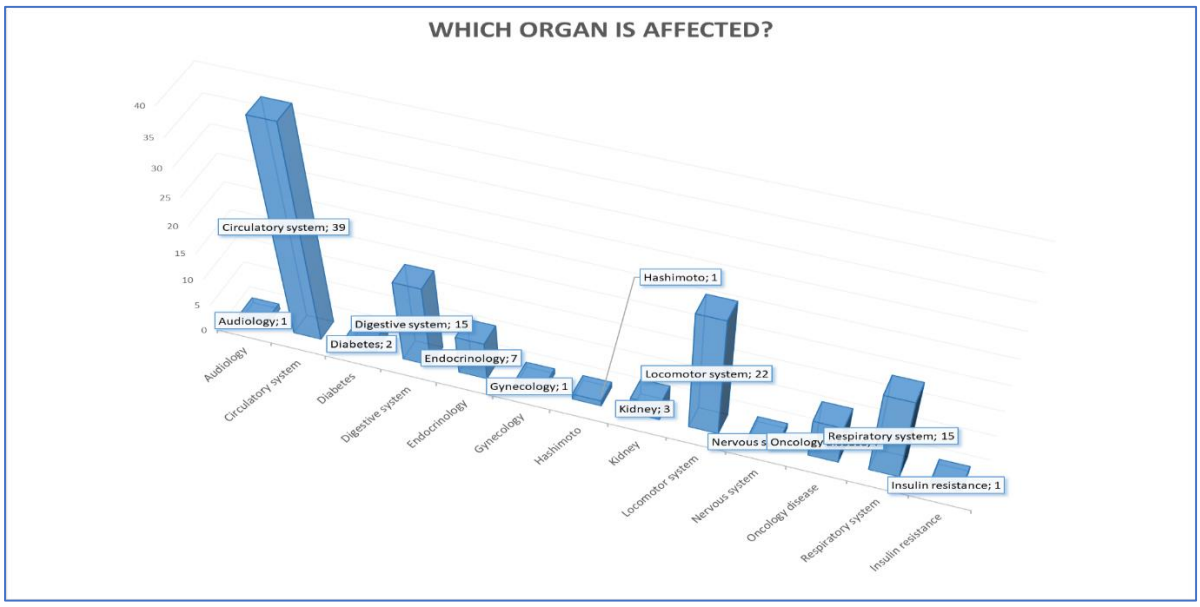
12. FIGURE, GROUP DISTRIBUTION BY CHRONIC DISEASE PATIENTS

Effected Organ of Chronic Disease

If we deeply analyze the chronic disease the following picture emerged. A total of 115 chronic diseases were reported. 72% (n=83) reported to have 1 effected organ, 23% (n=19) reported 2 effected organ, 9,6% (n=11) reported 3 effected organ, 1,7% (n=2) reported that 3 organs affected by chronic disease.

The distribution of the effected organ reported by participants are as follows: cardiovascular system (n=39), locomotor system (n=22), respiratory system (n=15), digestive system (n=15), oncology disease (n=7), endocrine disease (n=7), kidney disease (n=3), diabetes (n=2), insulin

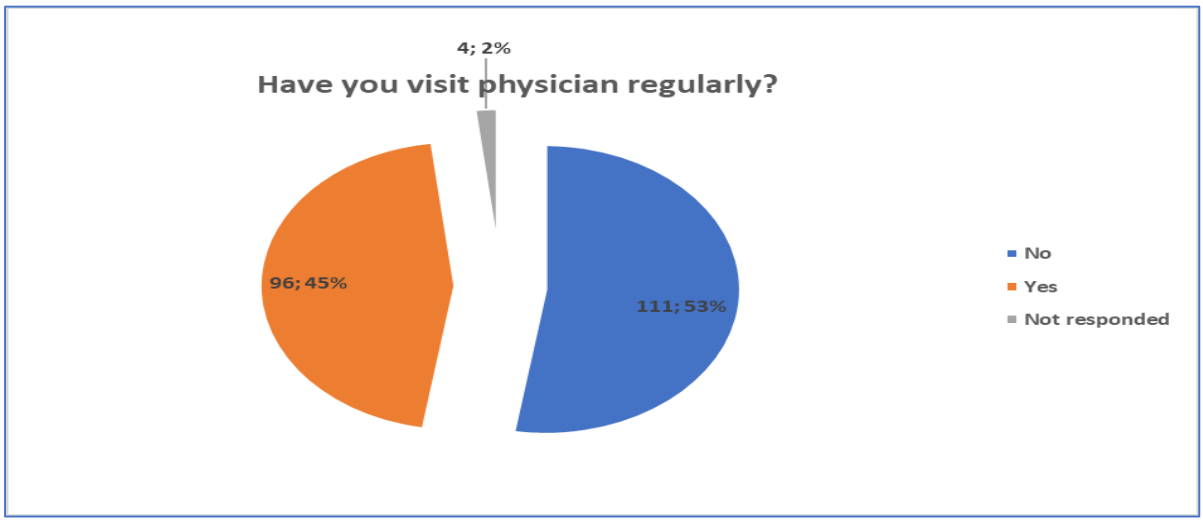
resistance (n=1), gynecology disease (n=1), auditory system (n=1), nervous system (n=1) and Hashimoto thyroiditis (n=1).



13. Figure, Which Organ is AFFECTED by Chronic Disease

Have you visit physician regularly?

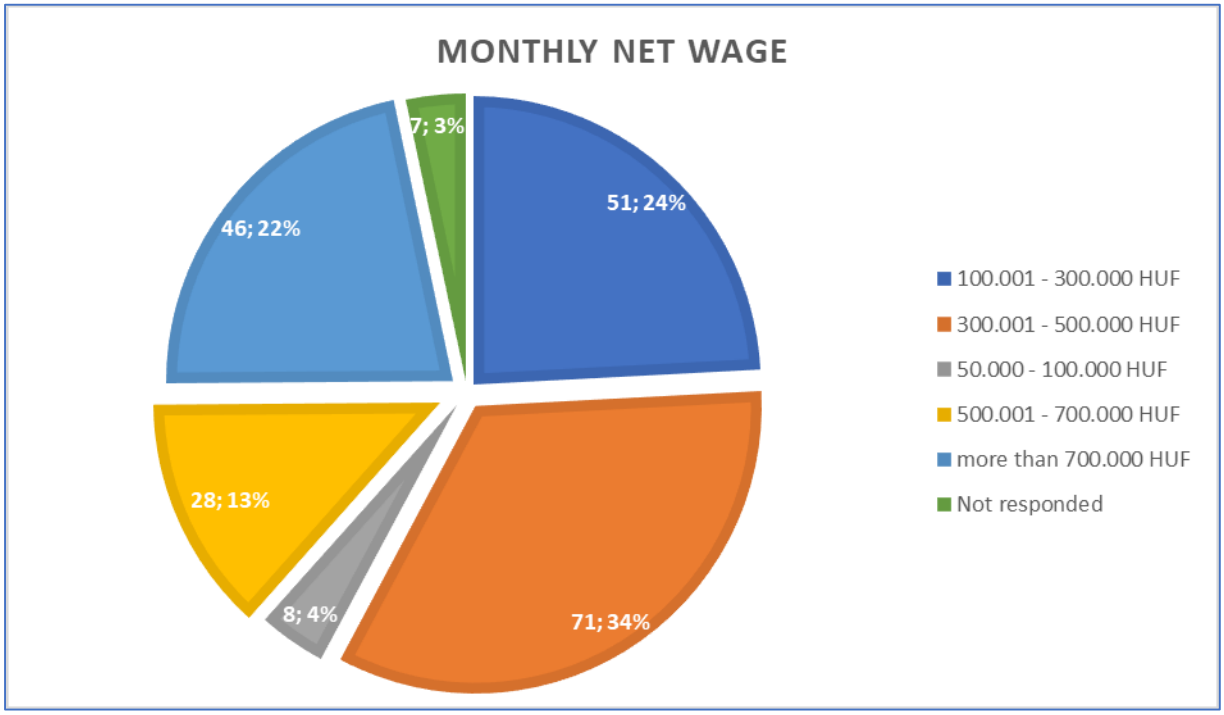
45% (n=96) reported visiting physician regularly and 53% (n=111) reported to not visiting. 2% (n=4) did not answer to the question.



14. Figure, Group Distribution of Subject Visiting Physician Regularly

Monthly net wage

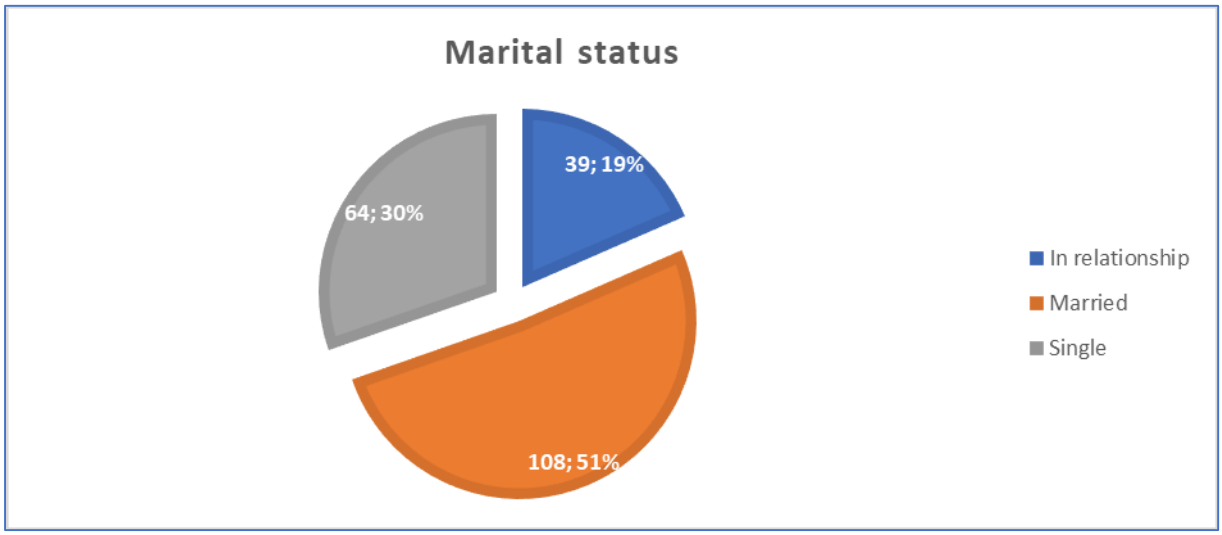
Concerning monthly net wage show us diverse picture. 46% (n=22%) reported net monthly wage more, than 700.000 HUF, 13% (n=28) reported wage in 500.001 - 700.000 HUF range, 34% (n=71) reported wage in 300.001 - 500.000 HUF range, 24% (n=51) reported wage in 100.001 - 300.000 HUF range, 4% (n=8) reported wage in 50.000 - 100.000 HUF range, and 3% (n=7) not answered to this question.



15. Figure, Group Distribution by Net Wage

Marital status

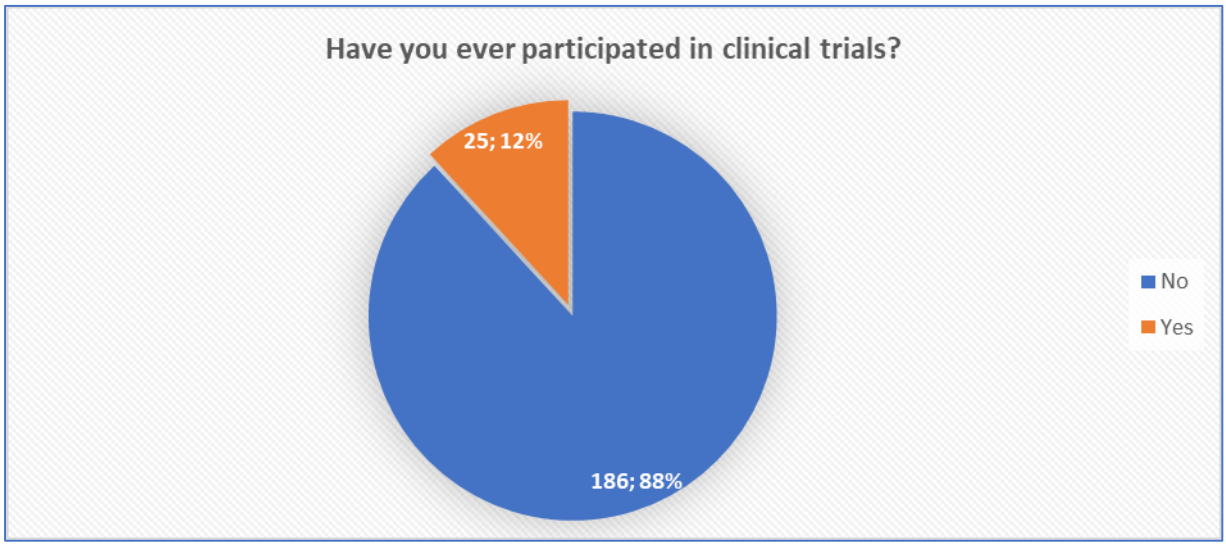
51% (n=108) of the participants live in a marriage, 19% (n=39) live in a relationship and 30% (n=64) reported to be single.



16. FIGURE, GROUP DISTRIBUTION BY MARITAL STATUS

Prior Clinical Study experience

According to subjects 88% (n=186) has never been a participant of clinical trial while 12% (n=25) did or currently participating in a clinical trial. This gives us the possibility to find out if there is any difference in between the 2 group in terms of knowledge on drug development process, willingness to participate in further clinical studies.



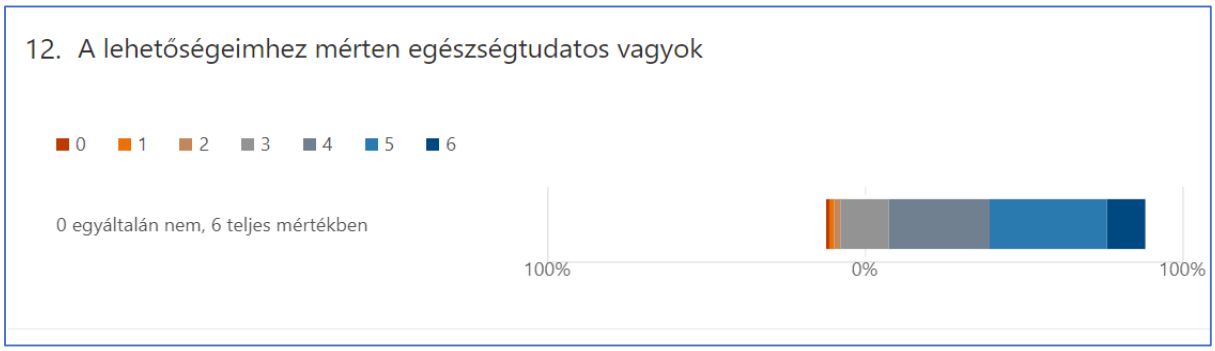
17. FIGURE, PRIOR CLINICAL STUDY EXPERIENCE

Investigating Exploration specific questions

This part of the Questionnaire is using 7-point Likert scale (please see Questionnaire in Appendix 1). The questionnaire was developed in a way to narrow the questions from general health consciousness to knowledge on clinical drug development throughout 7 questions. One question touch on the participant's opinion whether clinical studies are in the benefit of society or not in order to find out at the end if altruism is influencing the person's decision to participate in clinical trials.

Health Consciousness

According to the diagram below most of the responders state they are more health conscious as far as possible.

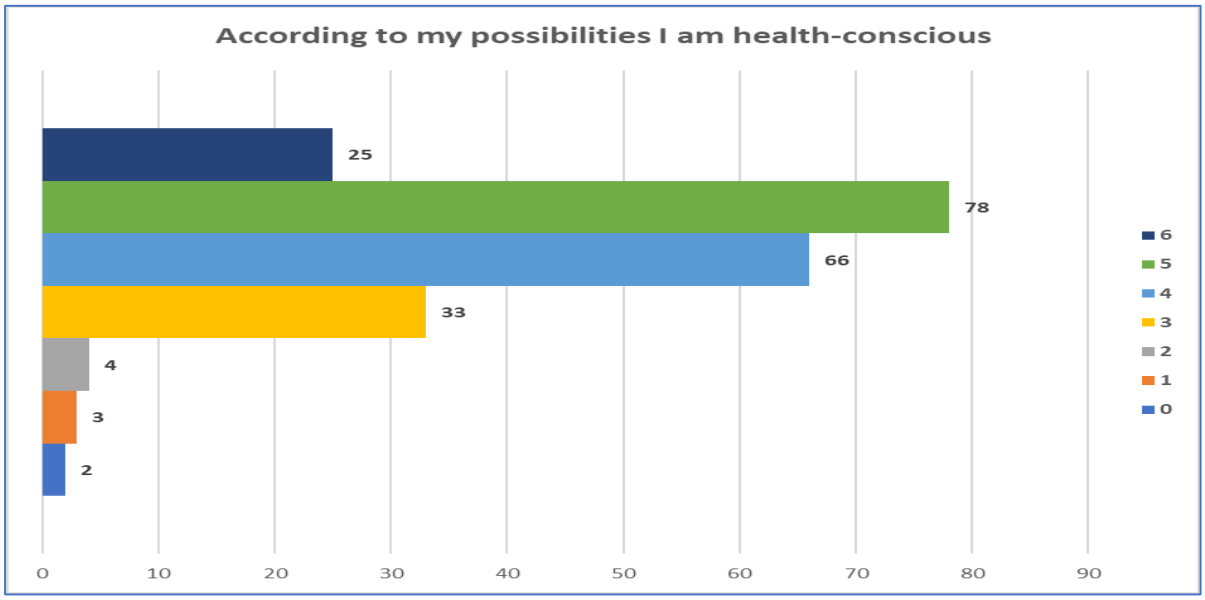


18. Figure, Health Consciousness, Captured Original Diagram from MS Forms

After analyzing the data set the following picture emerged whereas 0=not at all, 6=absolutely.

	Health cosciousness						
	Not at all						**Absolutely**
	0	**1**	**2**	**3**	**4**	**5**	**6**
n	2	3	4	33	66	78	25
%	0,95	1,42	1,90	15,64	31,28	36,97	11,85

19. Figure, Percentage and Distribution of Each Group, Health Consciousness

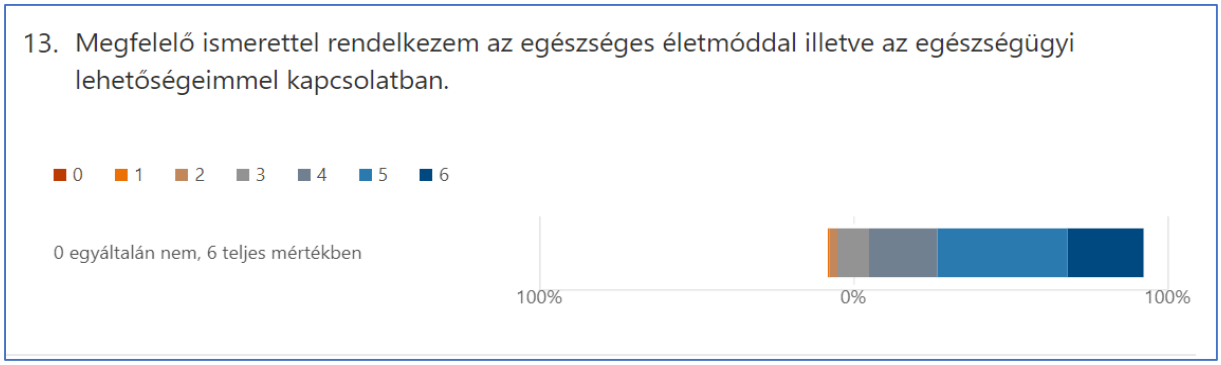


20. Figure, Group Distribution by Health Consciousness

Only a small percent of the responders stated that their health consciousness is “below average”. Most of the responders have average or above average health consciousness, while 11,85% (n=25) marked they are absolutely health conscious. We can state that the majority of the responders are very much aware of their options to live a healthy life. From the research point of view, it is expected that the subject population should be aware of all aspects of health including the proper use of available medication.

Healthy lifestyle and healthcare possibilities

Similar picture can be seen as the responses prior to “health consciousness” question.

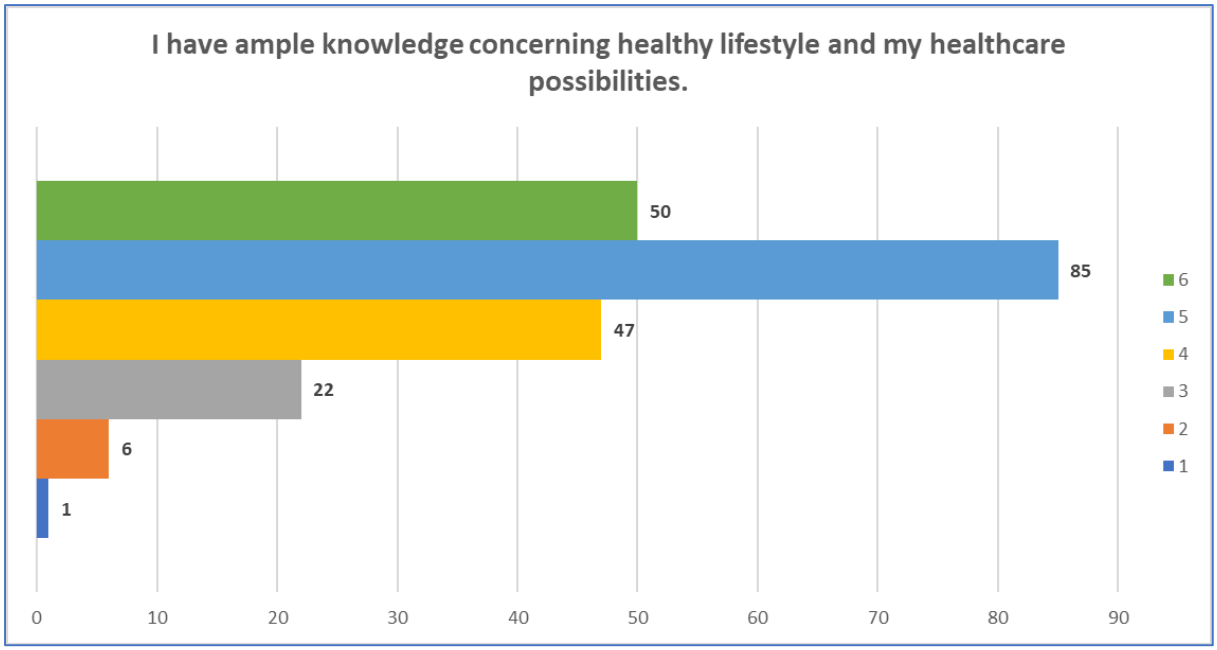


21. Figure, Healthy Lifestyle, Captured Original Diagram from MS Forms

	Ample knowledge on healthy lifestyle and healthcare possibilities						
	Not at all						Absolutely
	0	1	2	3	4	5	6
n	0	1	6	22	47	85	50
%	0,00	0,47	2,84	10,43	22,27	40,28	23,70

22. Figure, Percentage and Distribution of Each Group, Healthy Lifestyle

This data shows us that there is a correlation between general health consciousness and knowledge on healthy lifestyle and medical possibilities according to the responders. We must mention that in this question 0 responder indicated “not at all” option.



23. Figure, Group Distribution by Knowledge on Healthy Lifestyle

The data above indicates a population where most of them describe themselves having above average information and knowledge how to maintain and improve their health through lifestyle and medical system.

Knowledge on medications

Evaluating the next question, asking the subjects knowledge on medicines in general the data is similar than the previous 2 but some degree of decrease can be seen.

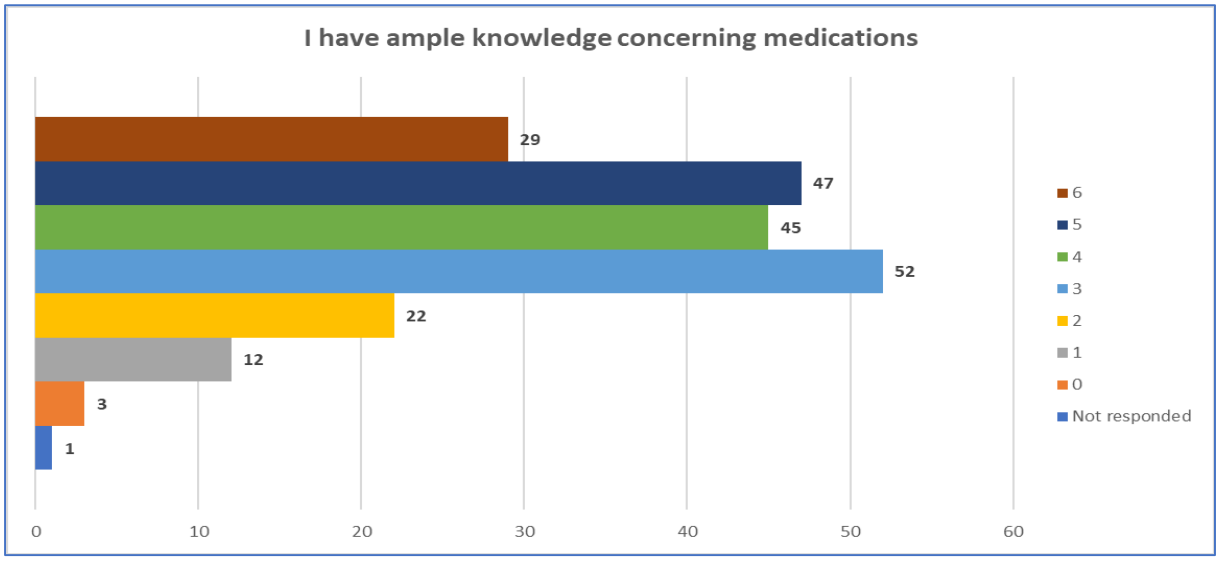
24. Figure, Knowledge on Medication, Captured Original Diagram from MS Forms

What does it mean in numbers?

	Ample knowledge on medication						
	Not at all						**Absolutely**
	0	**1**	**2**	**3**	**4**	**5**	**6**
n	3	12	22	52	45	47	29
%	1,43	5,71	10,48	24,76	21,43	22,38	13,81

25. Figure, Percentage and Distribution of Each Group, Knowledge on Medication

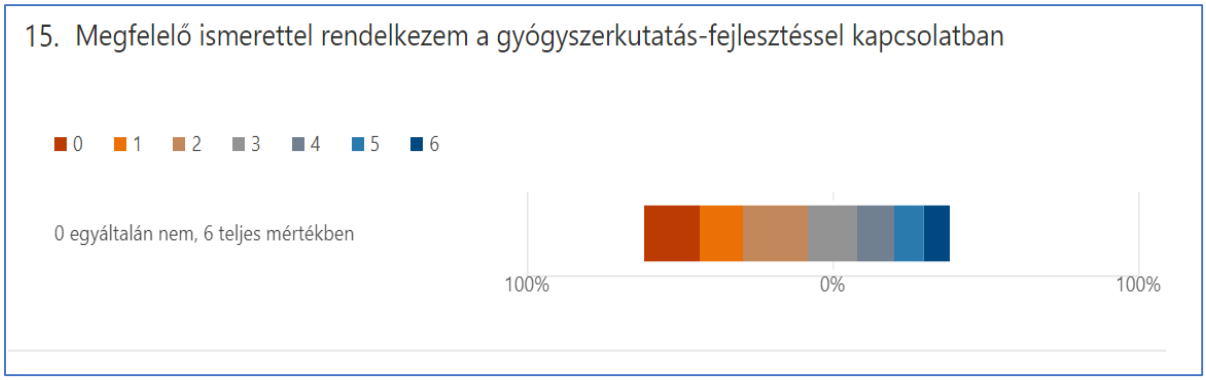
We can see some decrease in the top tier and the whole graph moving to the left indicating that most of the responders are closer to the "average" while the amount of "below average" is emerging. It is indicating that the amount of knowledge on medication is less in general compared to the healthy lifestyle and health consciousness.



26. Figure, Group Distribution by Knowledge on Medication

Knowledge on drug development

The next question is asking participant's knowledge on drug development in general. An interesting picture visible. While the majority of the partipants's knowledge on health, healthcare and health cosciousness was high in general, there is a significant decrease on reported knowledge on drug development.

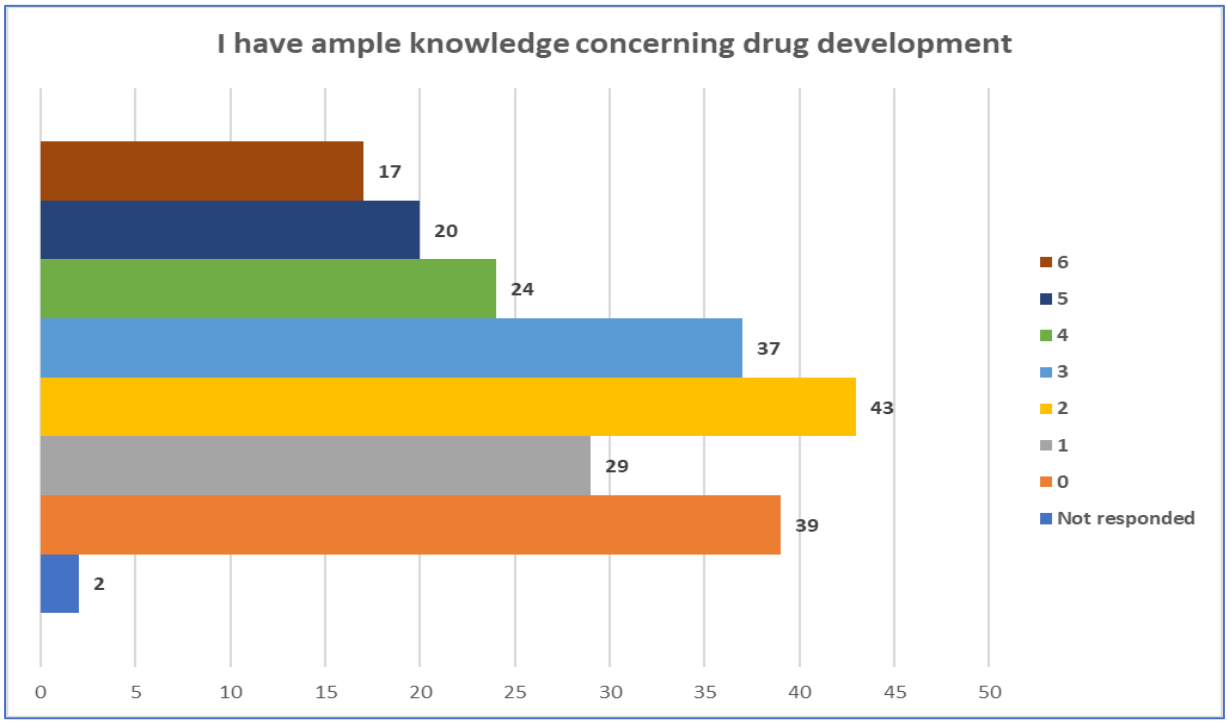


27. Figure, Knowledge on Drug Development, Captured Original Diagram from MS Forms

	Ample knowledge on drug development						
	Not at all						**Absolutely**
	0	**1**	**2**	**3**	**4**	**5**	**6**
n	39	29	43	37	24	20	17
%	18,66	13,88	20,57	17,70	11,48	9,57	8,13

28. Figure, Percentage and Distribution of Each Group, Knowledge on Drug Development

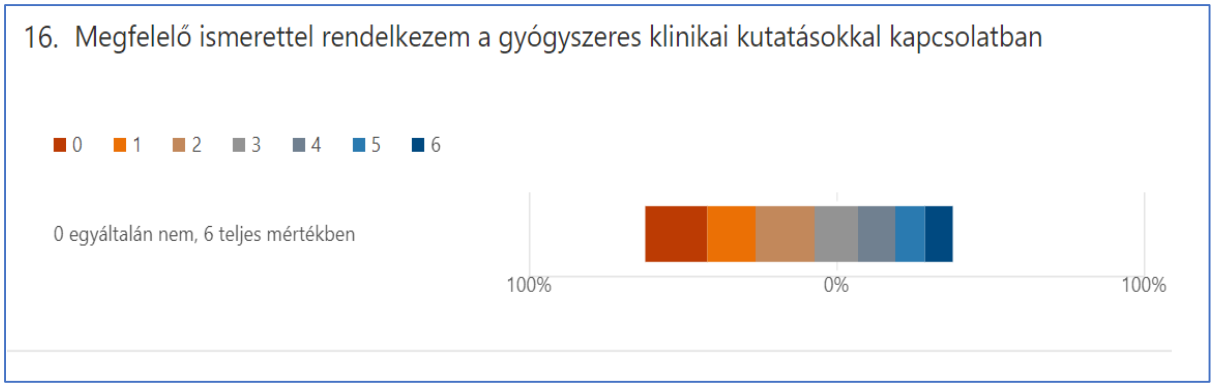
According to the numbers there was a significant decrease in the top 4 ratings while the bottom 3 ratings were increased. We can see that more than half of the responders (53,11%, n=111) have no or limited knowledge on medication development process. There were 2 subjects who did not respond to this question.



29. FIGURE, GROUP DISTRIBUTION BY KNOWLEDGE ON DRUG DEVELOPMENT

Knowledge on Clinical Trials

The next question is asking participant's knowledge on clinical trials. The picture visible became more interesting. While the majority of the particants knowledge on health, healthcare and health cosciousness was high in general, there is also a significant decrease in reported knowledge on clinical trials involving investigational product.

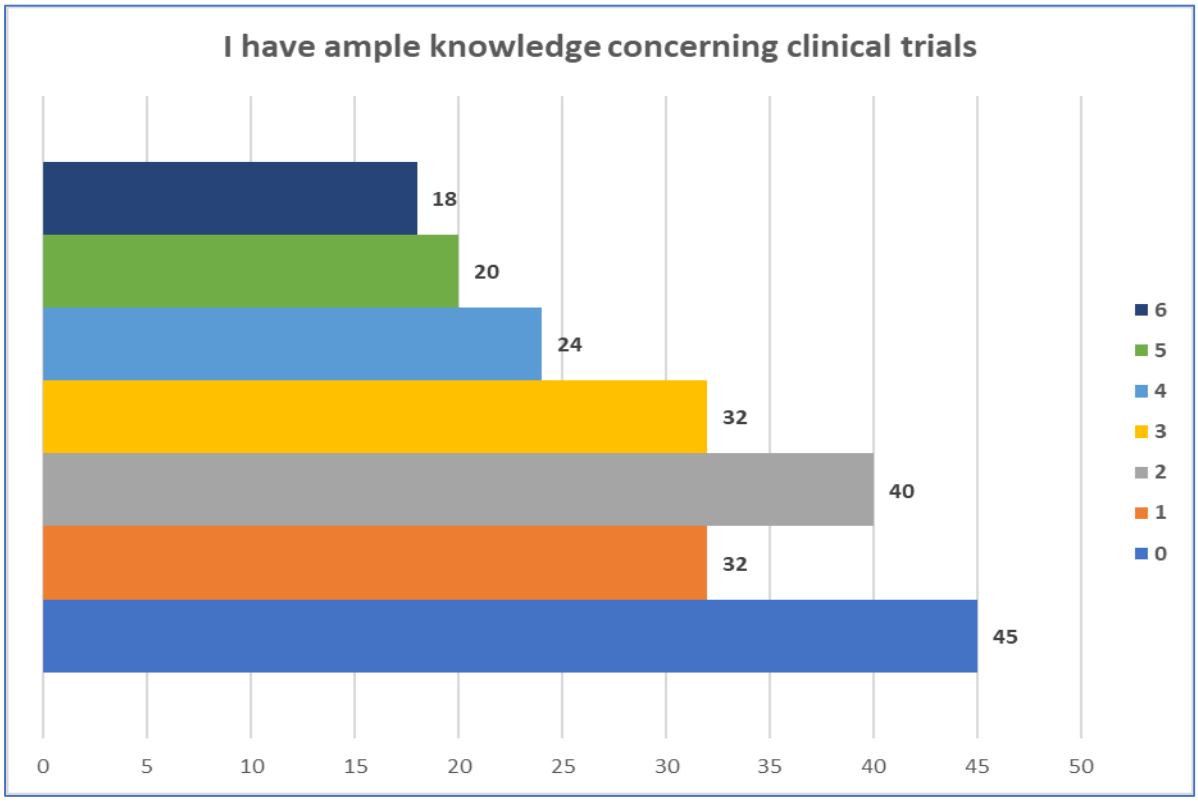


30. FIGURE, KNOWLEDGE ON CLINICAL TRIALS, CAPTURED ORIGINAL DIAGRAM FROM MS FORMS

	Ample knowledge on clinical trial involving investigational product						
	Not at all						Absolutely
	0	1	2	3	4	5	6
n	45	32	40	32	24	20	18
%	21,33	15,17	18,96	15,17	11,37	9,48	8,53

31. Figure, Percentage and Distribution of Each Group, Knowledge on Clinical Trials

According to the numbers there was a significant decrease in the top 4 ratings while the bottom 3 ratings were increased. We can see that more than half of the responders (55,46%, n=117) have no or limited knowledge on medication development process. The group of "not at all" contains ¼ of all responders 21,33% (n=45)

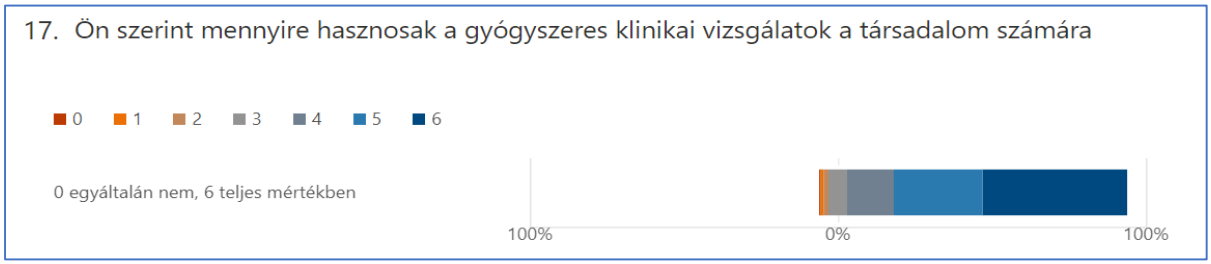


32. Figure, Group Distribution by Knowledge on Clinical Trials

Based on these numbers we can state that more than half of the responders are lacking confident knowledge on clinical trials involving investigational products.

Usefulness of Clinical Trials

From the exploratory research point of view, I wanted to find out the opinion of the participants whether or not they find the clinical trials useful for the society. An interesting picture appeared.



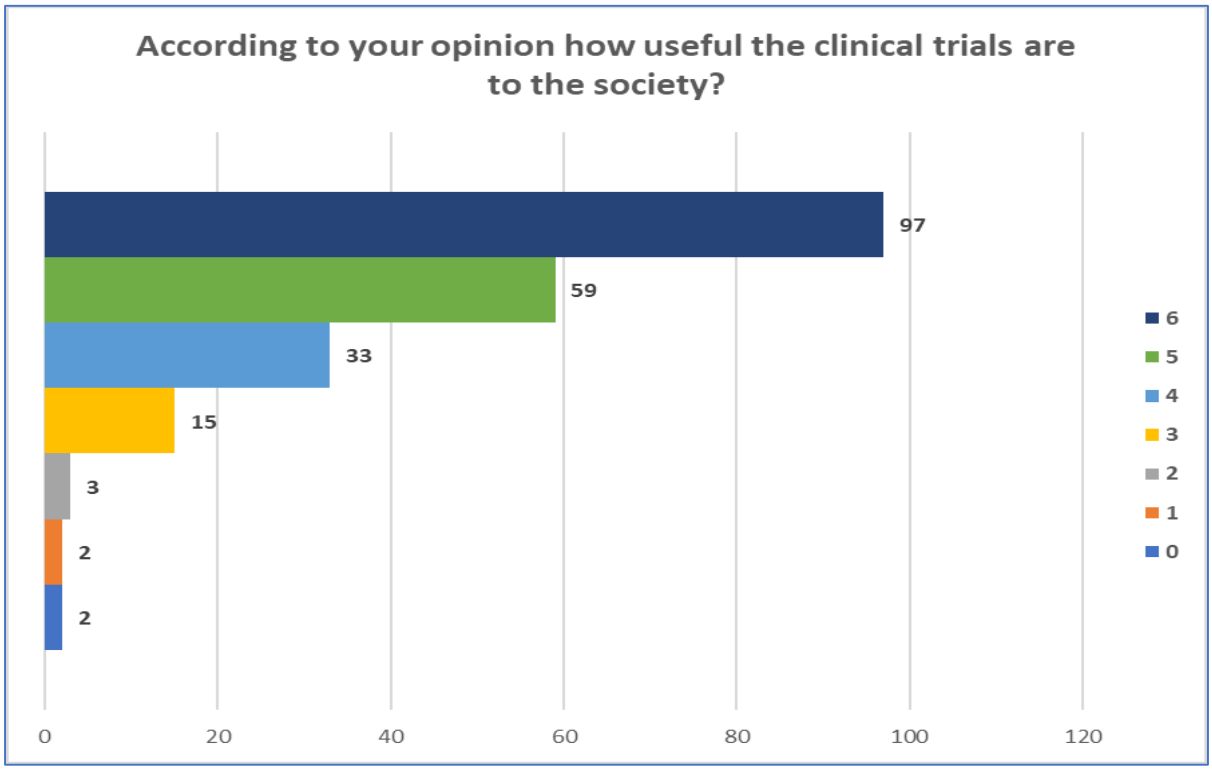
33. Figure, Usefulness of Clinical Trials, Captured Original Diagram from MS Forms

Most of the participants believed that the clinical trials have importance for the society. In numbers we can see the following.

	Usefulness of Clinical Trials for the Society						
	Not at all						**Absolutely**
	0	**1**	**2**	**3**	**4**	**5**	**6**
n	2	2	3	15	33	59	97
%	0,95	0,95	1,42	7,11	15,64	27,96	45,97

34. Figure, Percentage and Distribution of Each Group, Usefulness of Clinical Trials

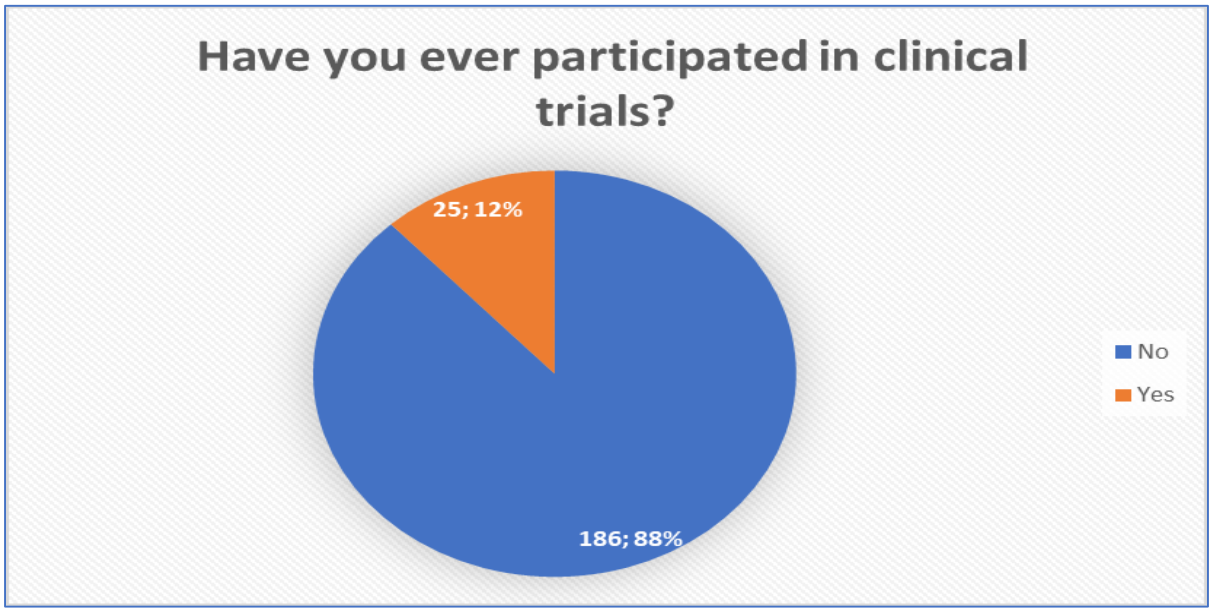
According to 45,97% (n=97) thinks that the clinical trials are “absolutely” useful for the society. The top 3 tier a sum of 89,57% (n=189) believes the clinical trials are useful for the society and only a small percent skeptic toward clinical studies. While the numbers of the supporters are high, we should cross check this data with previous data set on ample knowledge on clinical trials involving medicines which I will do later.



35. FIGURE, GROUP DISTRIBUTION BY USEFULNESS OF CLINICAL TRIALS

Have you ever participated in Clinical Trial

To shape the picture and lower the bias on data there was a question asking if the participants have ever taken part in clinical trial in the past. According to the data 12% (n=25) have already been participated in clinical trials while 88% (n=186) have never been participated in clinical trials.



36. Figure, Prior Participation in Clinical Trial

Likelihood of participation in Clinical Trials

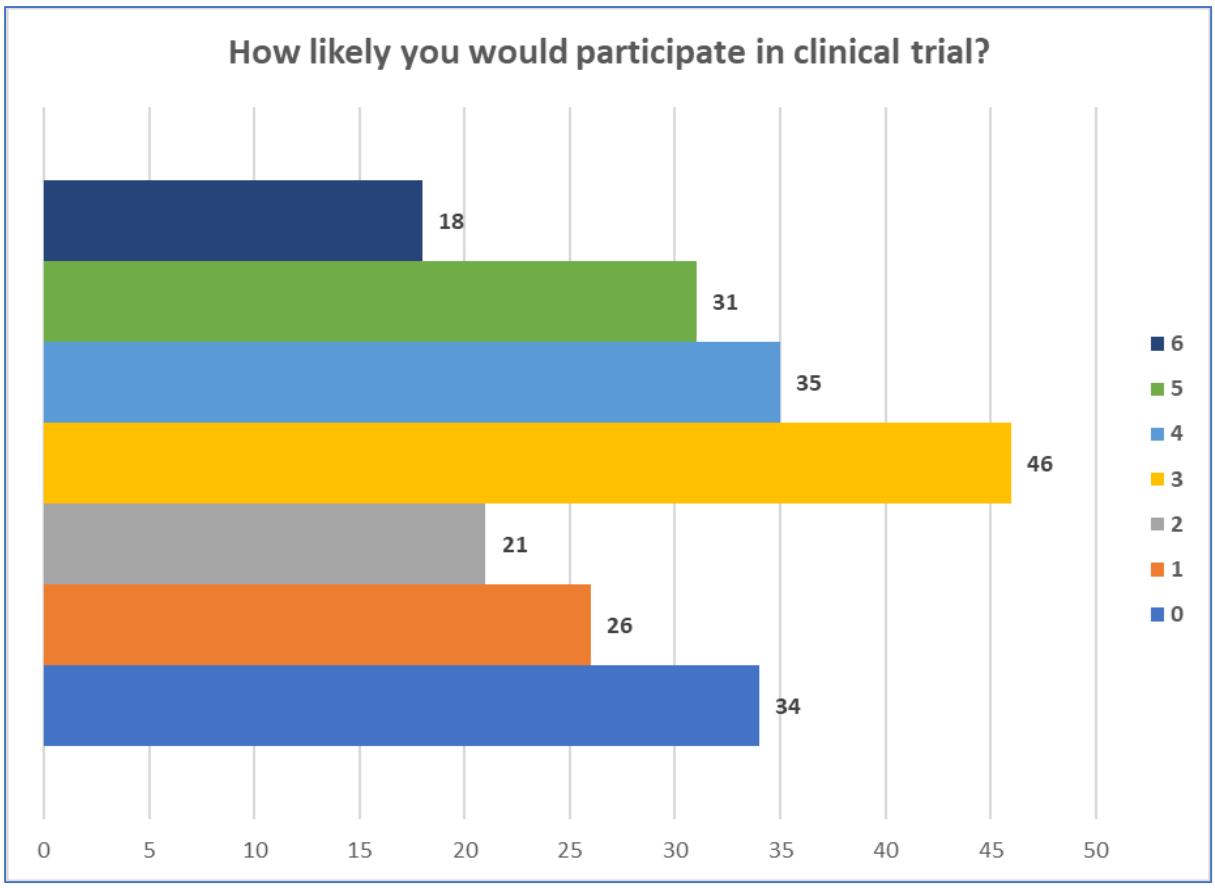
The investigation exploration now going down to personal level in a way to find out the participant willingness to be involved in clinical trials. The responses are showing us the following picture.

37. Figure, Likelihood of Participation, Captured Original Diagram from MS Forms

	Likelihood of participation						
	Not at all						Absolutely
	0	1	2	3	4	5	6
n	34	26	21	46	35	31	18
%	16,11	12,32	9,95	21,80	16,59	14,69	8,53

38. Figure, Percentage and Distribution of Each Group, Likelihood of Participation

According to the data the “neutral” answer is the biggest group here with 21,8% (n=46) and only 8,53% (n=18) indicated their likelihood of participation as “absolutely”, while 16,11% (n=34) indicated “not at all”. While the top 3 tier of responders are indicated clinical trials are useful for the society there is less likelihood of willingness to participate appears here.

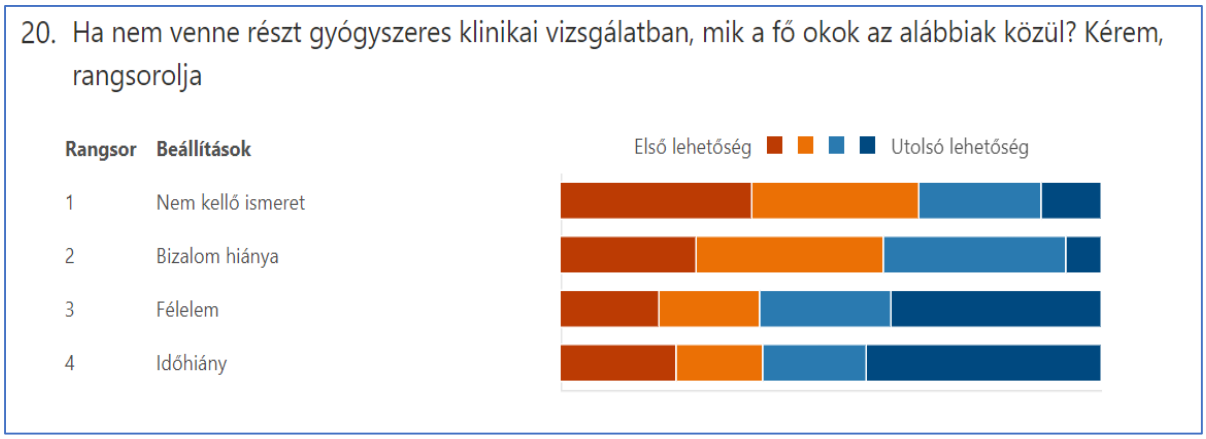


39. Figure, Group Distribution by Likelihood of Participation

Reason why not to participate

Not to participate in a clinical study is a personal decision but can be based on varied factors. According to my 20+ years of experience I put together 4 main reasons (lack of knowledge, lack of trust, fear, lack of time) and asked the participants to rank these factors.

The following picture appears.



40. Figure, Reason for Not Participating, Captured Original Diagram from MS Forms

	Rank 1	Rank 2	Rank 3	Rank 4
Lack of knowledge	**35,30%**	30,90%	22,80%	11,00%
Lack of trust	25,00%	**34,60%**	**33,80%**	6,60%
Fear	18,40%	18,40%	24,30%	39,00%
Lack of time	21,30%	16,20%	19,10%	**43,40%**

41. Figure, Percentage and Distribution of Each Group, Reason for Not Participating

According to data analysis the ranking is the following:

1, Lack of knowledge

2, Lack of trust

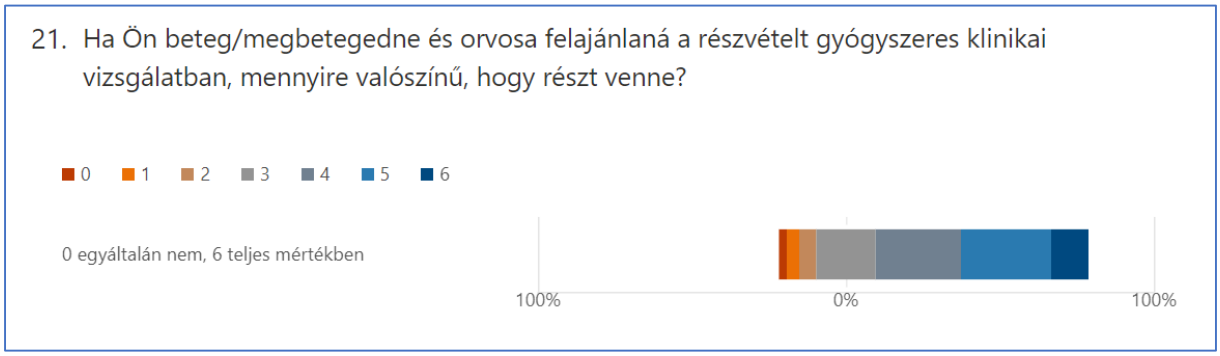
3, Fear

4, Lack of time

Interestingly lack of knowledge and lack of trust are the main factors preventing someone from participating in clinical trials.

Likelihood of participation as ill patient

This question is more specific to the subject. If the subject became ill and his/her physician offered participation in a clinical trial aiming at the specific disease, what is the probability of being engaged. According to the responses the scale is pushed more to the positive side.

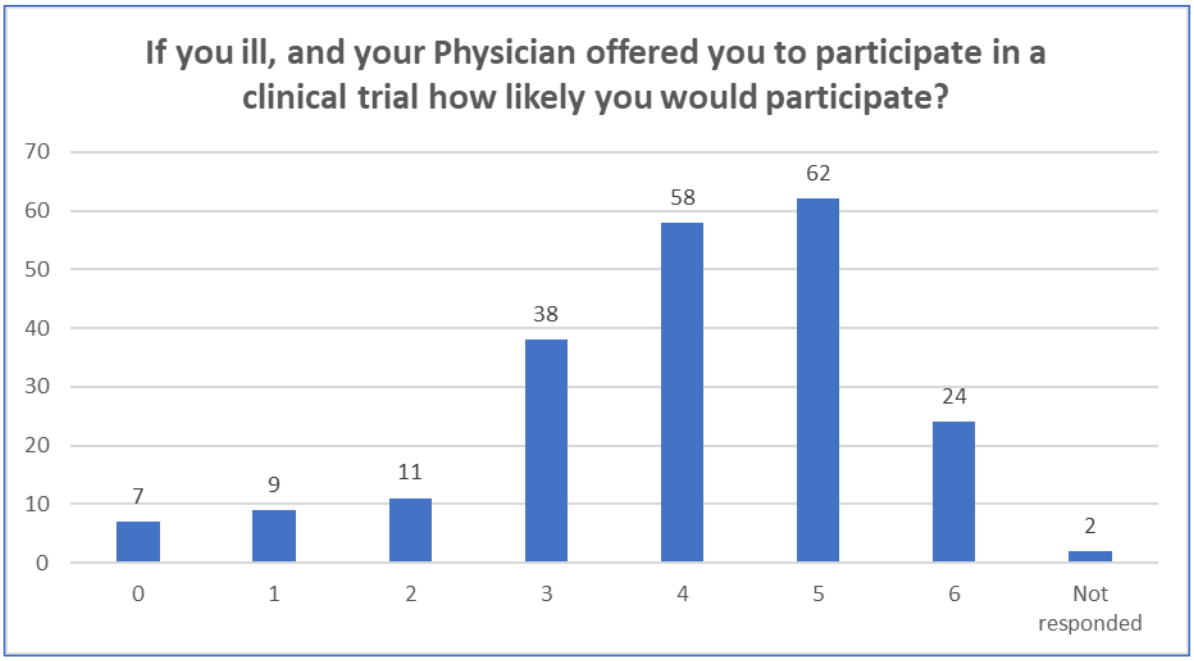


42. Figure, Reason for Not Participating, Captured Original Diagram from MS Forms

	Likelihood of participation as ill patient						
	Not at all						**Absolutely**
	0	**1**	**2**	**3**	**4**	**5**	**6**
n	7	9	11	38	58	62	24
%	3,35	4,31	5,26	18,18	27,75	29,67	11,48

43. Figure, Percentage and Distribution of Each Group, Likelihood of Participation as Ill Patient

As we can see the majority of the participants 68,9% (n=144) were on the positive side, which means they would rather participate in a clinical study if they became ill. I must mention that 18,18% (n=38) were neutral to this question and only 12,92% (n=27) answered negatively about participation.



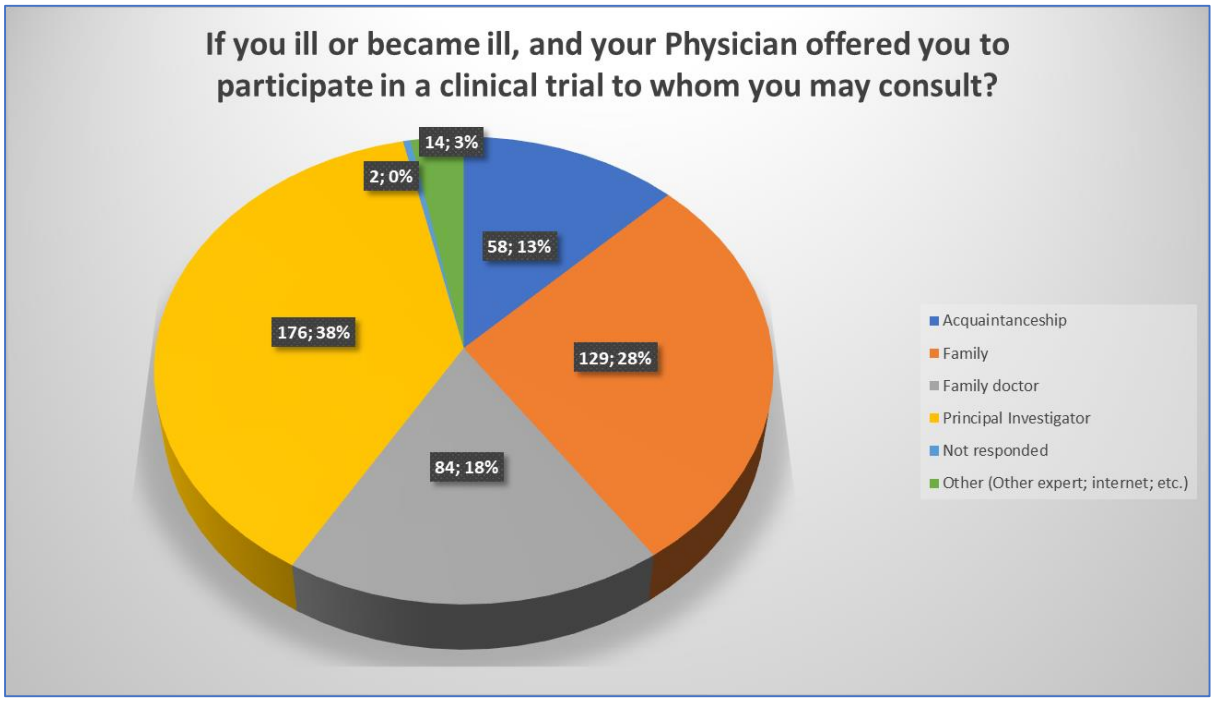
44. Figure, Group Distribution by Likelihood of Participation as Ill Patient

Exploring the reasons

The last 9 question in the Questionnaire is developed in a way to find out those factors which 1, drive the potential clinical trial participants to join in a clinical study and 2, which are the main and reliable sources where potential trial participants expect to gather information. The following picture emerges.

Discussion before participation

One major element of the process during clinical trial is the informed consenting process. During this process, the subject is provided with an Informed Consent document during a discussion with the Principal Investigator. The subject is also offered time to discuss to whom he/she relies on. In this question I explore the sphere of those sources which the participants considered as reliable sources for additional consultation before making the decision. For this question, the participants were to answer multiple choices.



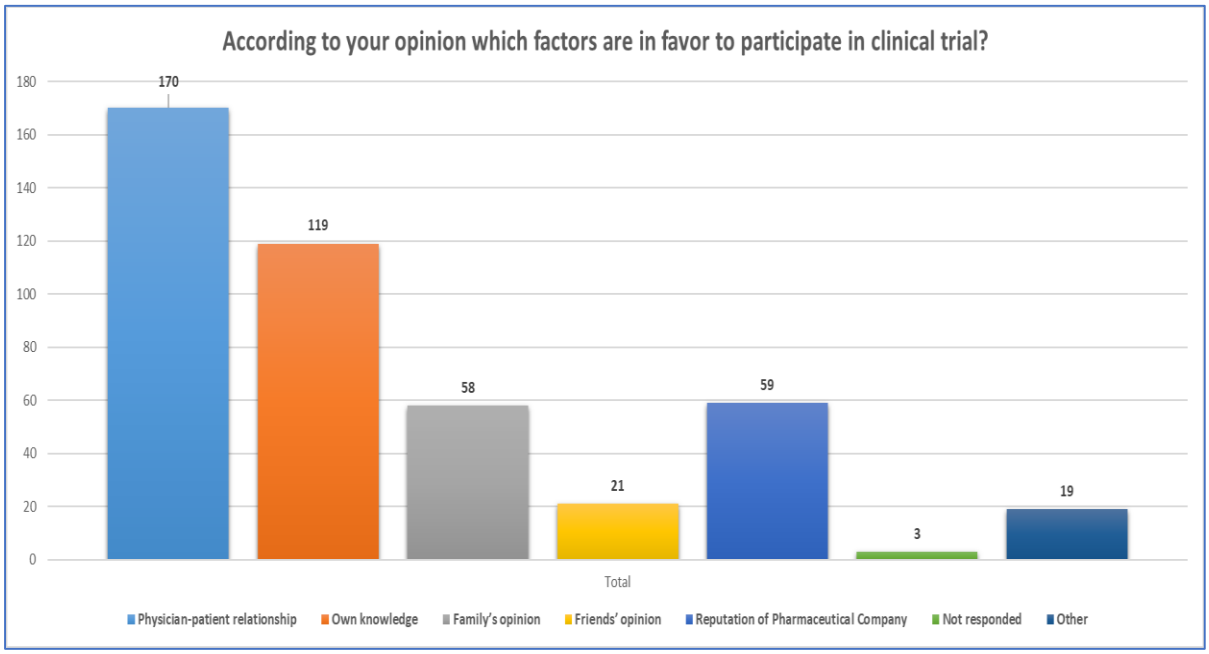
45. FIGURE, GROUP DISTRIBUTION BY TO WHOM THE SUBJECT CONSULT BEFORE PARTICIPATION

According to the responses the main source of information would be the Principal Investigator 38% (n=176). The second is the family 28% (n=129), third is the General Practitioner 18% (n=84) and fourth source of information is the Acquaintanceship 13% (n=58). I must mention that some of the participants lived with the free text (Other, please specify) option indicating they would check the internet, discuss with other experts or those who already participated in clinical trials.

Factors pro clinical study participations

This question is aiming those factors which influence one's intent to participate in clinical trials. Why is it important?

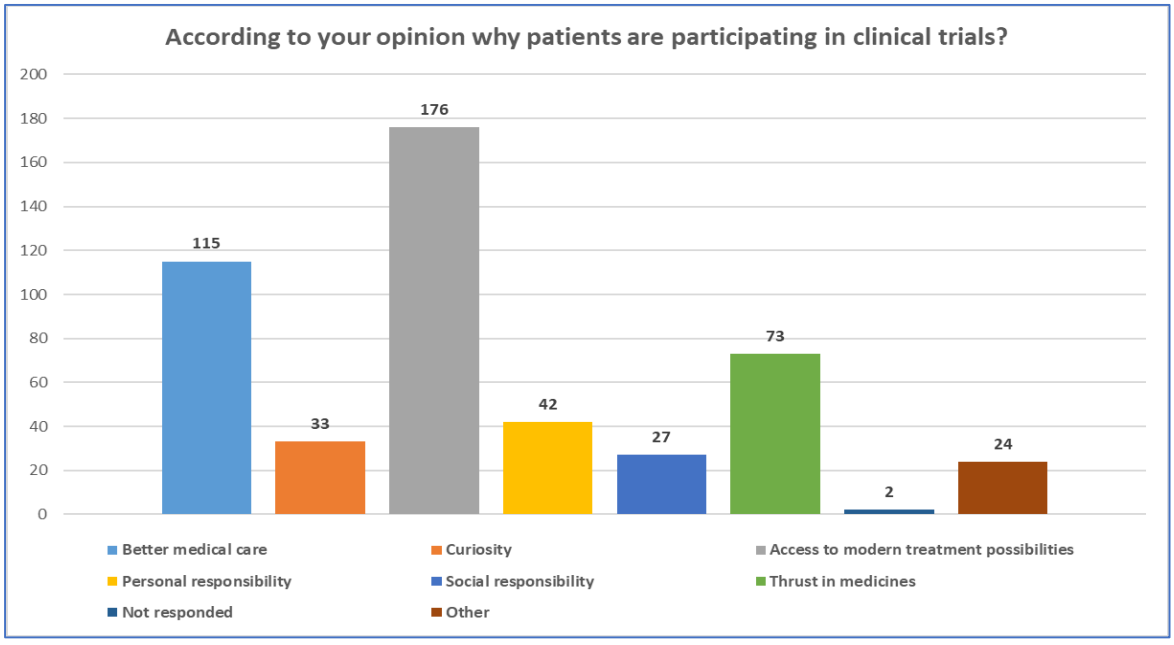
The 2 major answer for this question are 1, the patient physician relationship which is based on trust and knowledge of the medical doctor; 2, the potential participants own knowledge. It also must be mentioned there is also two more factors which influence the decision which less but equally important. The first is the Family's opinion and the second is the reputation of the Pharmaceutical Company carrying out the study.



46. FIGURE, GROUP DISTRIBUTION BY FACTORS FAVOR TO PARTICIPATION

Why to participate in clinical trials as patient

During decision making there are several factors that may come up. Multiple answers were accepted for this question where the following picture appears.



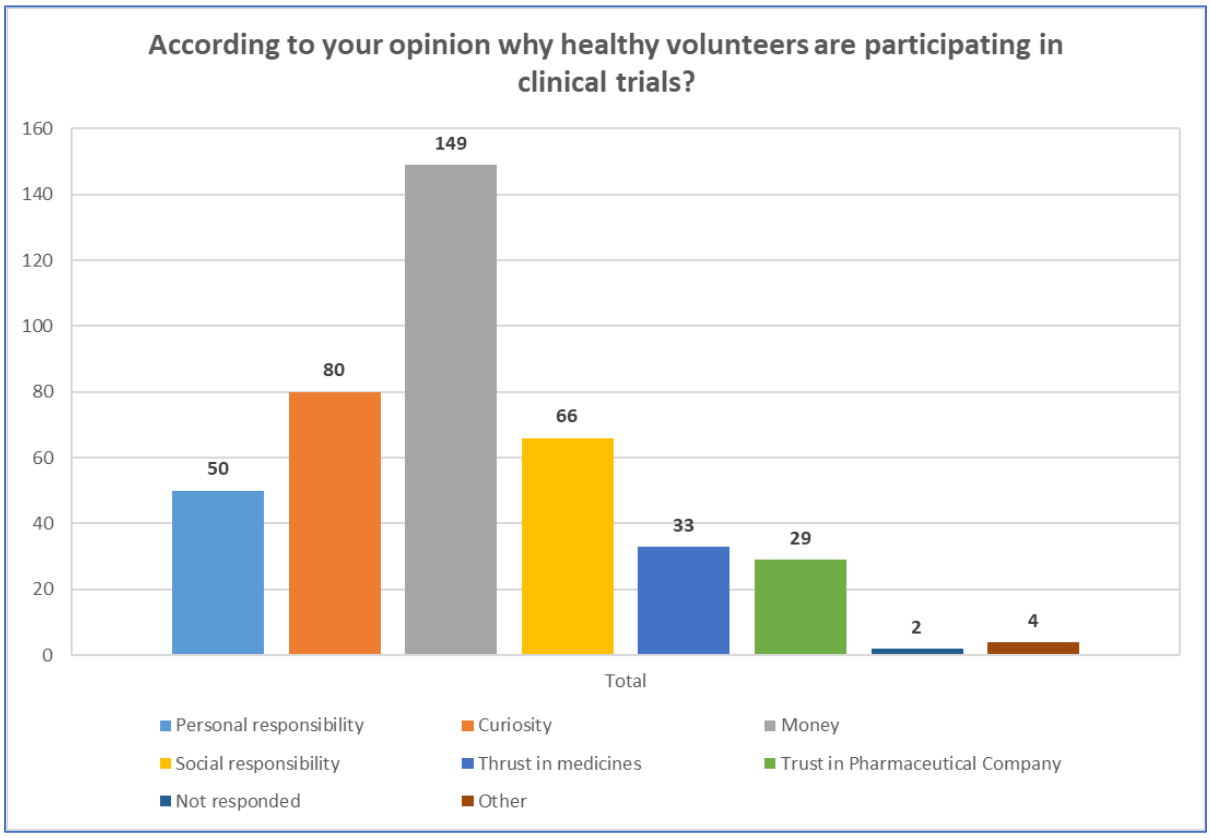
47. FIGURE, GROUP DISTRIBUTION BY REASONS FOR PARTICIPATION IN CLINICAL TRIALS

176 response indicates that “Access to modern treatment possibilities” are the main factor. 115 response indicates “Better medical care”, 73 response indicates “Thrust in medicines”. It shows us that most of the answers are about medical care.

Although it must be mentioned that a total of 75 responses indicate personal or social responsibility.

Why to participate as healthy volunteer in general

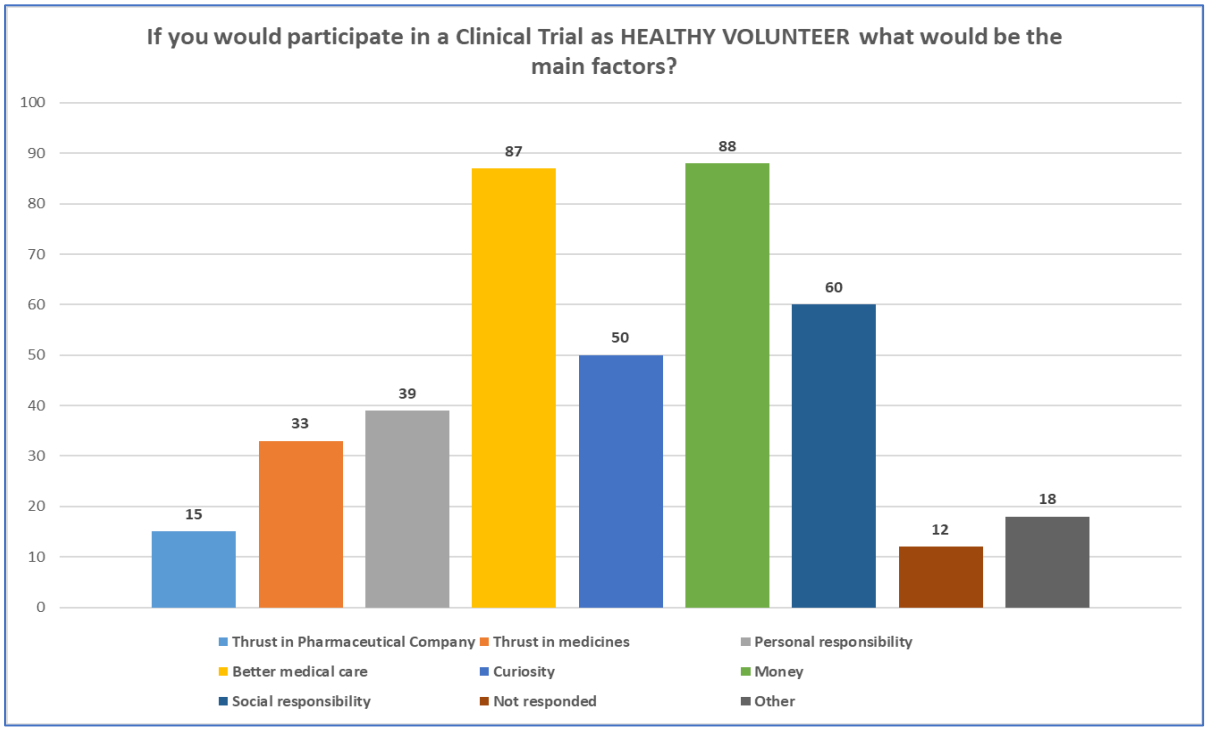
There are separate questions for healthy volunteers. I added this question as according to Hungarian law healthy volunteers can be paid for participation in early phase clinical studies, so the money as potential incentive can come into the picture. This might not be applicable to all Countries.



48. FIGURE, GROUP DISTRIBUTION BY REASON FOR PARTICIPATION AS HEALTHY VOLUNTEER

The question asking participants in general shows remarkably interesting picture appears: n= 149 responder indicates “Money” in the first place, followed by “Curiosity” (n=80) and “Social responsibility” (n= 66) and “Personal responsibility” (n=50).

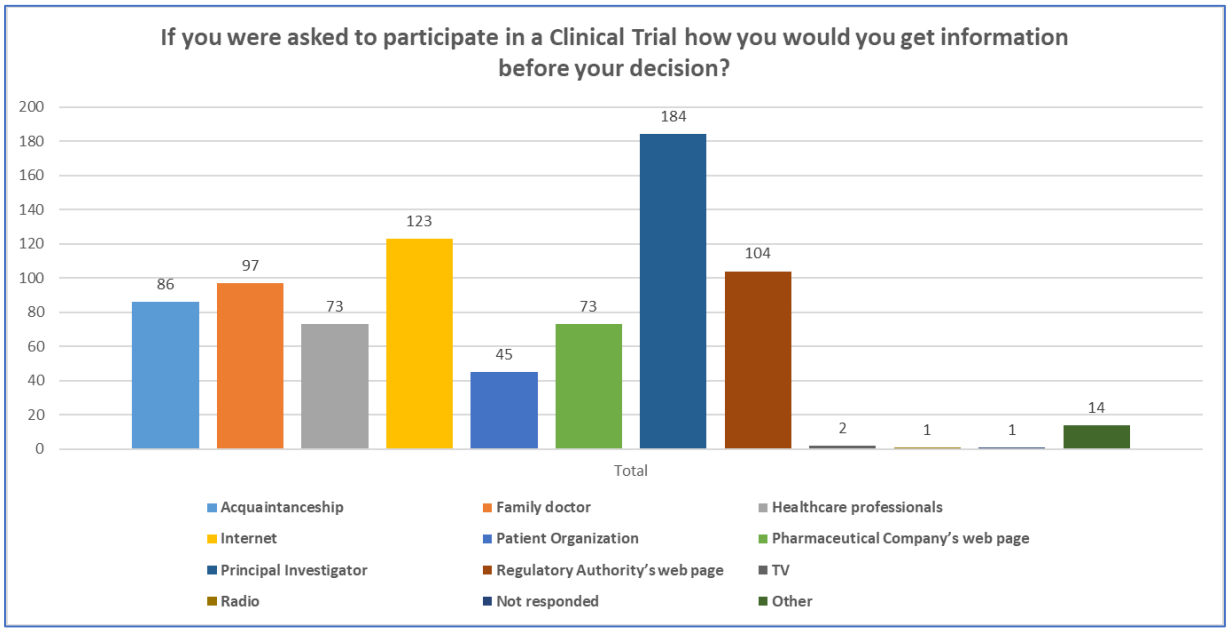
If the question goes down on a personal level asking the participants if they were offered to participate in clinical study as healthy volunteer the following appears. Money as main motivating factor decreased (n=149 vs n=88) while the main motivating factor became “Better medical care” n=87. “Curiosity” as main motivating factor also decreased (n=80 vs n=50) as shown below.



49. Figure, Group Distribution by Reason for Participation as Healthy Volunteer

Information Sources

As an important step before making a serious or life affecting decision to participate in a clinical trial needs careful consideration. This decision needs to be based on reliable information. The question is trying to explore the main information sources uses by the participants.



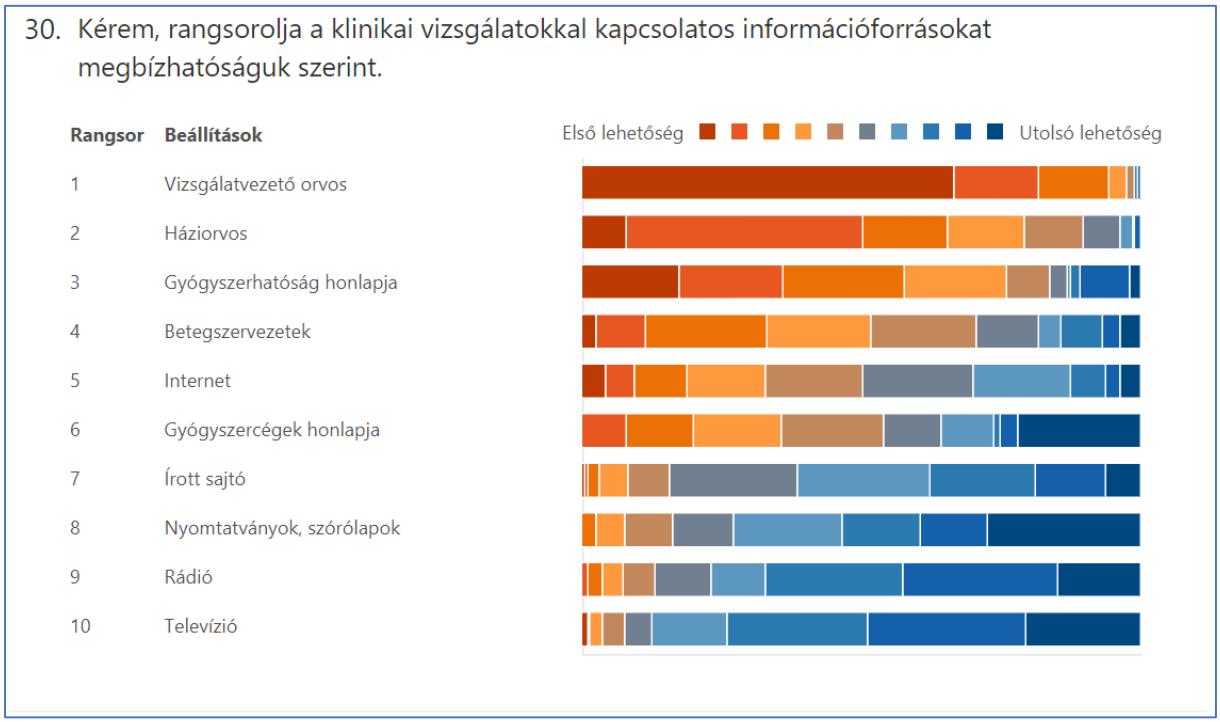
503. FIGURE, GROUP DISTRIBUTION BY INFORMATION SOURCE

According to the participants the first source of information would be the Principal Investigator (n=184). The second source of information is the Internet (n=123) and the third source would be the web page of the Regulatory Authority (n=104).

It is also neccesary to mention that there were 3 different questions (Internet, webpage of the Regulatory Authority and web page of the Pharmaceutical Company) where we can extend and say „internet altogether" represents the majority of all answers (cumulative n=300). Family (n=86), General Practitioner (n=97), healthcare professionals (n=73) and Patient Organizations (n=45) also represent another major portion of the responses.

Trustworthiness of information sources

The participants were asked to rank the information sources by the level of reliability.



51. Figure, Ranking of Source of Information by Reliability, Captured Original Diagram from MS Forms

	Most reliable							Least reliable		
Information sources by rank (n)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
General Practitioner (Family doctor)	18	**87**	29	27	21	13	4	1	2	0
Internet	8	10	20	30	33	39	36	12	5	9
Patient Organizations	5	18	**43**	**37**	**40**	21	9	16	6	7
Pharmaceutical Companies website	0	15	26	31	37	21	19	3	6	44
Principal Investigator	**134**	31	24	7	3	1	0	1	1	0
Printed media	1	1	4	10	15	**49**	**47**	38	25	12
Radio	0	2	5	8	13	19	19	48	**57**	31
Regulatory Authority website	34	38	44	38	15	6	1	3	19	4
Sheets, flyers	0	0	5	10	17	22	40	30	24	**54**
TV	2	0	2	4	8	11	27	**50**	**57**	41

52. Figure, Percentage and Distribution of Each Group, Reliability of Information Source

According to the participants, the following hierarchy appears. 1 represent the most reliable source, while 10 is representing the least reliable one:

1, Principal Investigator

2, General Practitioner (family doctor)

3, Website of the Regulatory Authority

4, Patient Organizations

5, Internet

6, Website of the Pharmaceutical Companies

7, Printed newspaper

8, Sheets, flyers

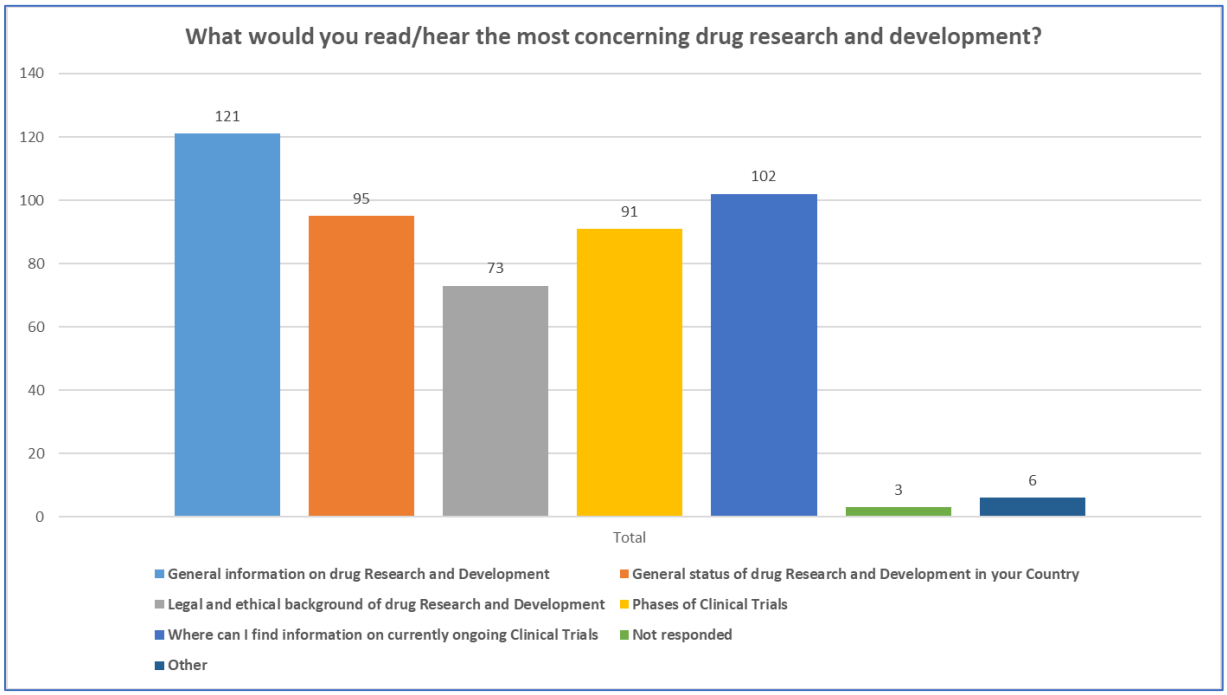
9, Radio

10, Television

Corresponding to the results most of the responders rely on the healtcare professionals (including Patient Organizations) and the Regulatory Authority the most, while the traditional information sources (TV, printed media) are considered the least reliable. The Internet (in general) and the website of the Pharmaceutical Companies represent average reliability.

What to hear and/or read about Drug R&D

The Questionnaire asks the participants what they would hear/read the most concerning drug research and development. There were pre-selected options with the possibility to choose „Other, please specify" alternative.



53. FIGURE, GROUP DISTRIBUTION BY INFORMATION PREFERENCE ON DRUG R&D

According to the responders they would hear/read about general information on drug R&D (n=121), where can they find information on ongoing clinical trials (n=102), general status of drug R&D in your country (n=95), phases of clinical trials (n=91), legal and ethical background of clinical trials (n=73). Concerning the „Other, please specify" option for the following responses were given (n=6):

„I do not care"
„What are the warranties of the presented results"
„Result of clinical trials"
„Expected side effects and how to prevent those. Further aim of drug development and results"
„Result of drug R&D abroad"
„Hard to answer, so far I do not interest in this topic"

Interestingly there was only 1 response aiming at the potential side effect(s) of the drug inder development.

While the majority of the participants indicated they are health-conscious, and they have ample knowledge on healthy lifestyle and healthcare options (Figure 21) they have limited knowledge on medications (Figure 24) and even less knowledge on drug development process (Figure 27) and clincal trials (Figure 30). Although they believe that the clinical trials involving medication are important to the society (Figure 33)

While the participants believe the clinical trials are important to the society the general willingness to participate is mediocre (Figure 37). The main reason of the unwillingness to participate in clinical trials are the lack of knowledge (Figure 40) which correlates the responses given to the question asking the participants about their knowledge on drug development and clinical trials (Figure 24, Figure 27).

My hypothesis is supported by this data, and we can say that one of the main reason for the slow recruitment might be the lack of knowledge of potential clinical trial subjects preventing them to make positive decision.

The statistical analysis conducted in this PhD dissertation serves as a robust foundation for drawing meaningful conclusions. Through the application of advanced statistical methods, key patterns and relationships within the data have been unveiled. The significance of various variables has been assessed, contributing to a comprehensive understanding of the research questions at hand.

The findings consistently align with the research hypotheses, providing dedicated support for the proposed theories. Moreover, the confidence intervals offer a level of precision that enhances the reliability of the results. The nuances captured in the data underscore the complexity of the phenomena under investigation.

It is essential to acknowledge the limitations of the statistical analysis, such as potential biases (e.g.: education, healthcare background) and assumptions inherent in the chosen methodologies. These considerations provide avenues for future research to refine and expand upon the current study.

In summary, the statistical analysis presented in this dissertation not only validates the research hypotheses but also illuminates the intricate dynamics within the dataset. This statistical rigor strengthens the overall contribution of the study to the existing body of knowledge in the field. Although it might be expressed, that the questionnaire used during this dissertation is not validated and might not representative.

VII. Recommendations

Based on my research the education on drug development and clinical trial involving medication should be increased among the population. This education should come from reliable sources. What is considered as reliable sources?

According to the responses the top 4 reliable sources of information are 1, Principal Investigator, 2, General Practitioner (family doctor) 3, The web page of the competent Regulatory Authority 4, Patient Organizations.

1, Principal Investigator

Principal Investigator is a highly qualified medical doctor who is carrying out clinical trials according to laws, regulations, and ethical standards. Since these healthcare professionals are expert and by occupation, they are leading clinical studies their knowledge is ample concerning this topic. Therefore, involving them into the education/information sharing would be useful.

2, General Practitioner (Family Doctor)

This is the first layer of healthcare system and has access to great percent of the population via their practice. According to my experience there might be two groups of General Practitioners (GPs). The first group of General Practitioners are those who also involved in clinical trials; therefore, they have ample knowledge, whilst the second group are research naïve professionals. Their knowledge advisable should be increased with up-to-date information on clinical trials and drug development which they can they regularly share with patients during their visits. It is also worth considering providing them with educational materials composed on a way to be understandable by wide part of the population. If they are active on internet/social media time after time they should share some educational materials

if their time permits. They should also educate their patient/relatives where they can find the Regulatory Authority's web page for most authentic source information.

3, Website of Regulatory Authority

It seems that there is a need to have information/educational material available on the web page of the Regulatory Authority. This information should be posted there in a way to be widely understandable by the lay population. The Regulatory Authority's webpage should be the first step to check by those who are interested in the topic. This should also include the highlight of the Clinical Trial legislation and those standards which protect clinical trial subjects' safety and well-being. If it highlights the strict regulatory approval and oversight process during the flow of full drug development, it might increase the willingness of patient participation.

In the European Union a website exists where the clinical trials are posted (www.clinicaltrials.gov) consisting of information about all registered clinical trials with actual statuses (recruiting, ended, not yet recruiting, approved etc.) but it is in English therefore translated to local language would be useful.

4, Patient Organizations

Similarly, to General Practitioners, Patient Organizations can also be involved in the education of population. It is understandable that there should not all disease suffering patient related Patient Organization exist but their commitment toward clinical studies and information sharing should be increased. This should be performed by involved physicians, Regulatory Authority and Pharmaceutical Companies.

What educational material should it be used?

The top 3 topic in favor of the participants are 1, General knowledge on drug development process, 2, Where to find information about running clinical trials and 3, General status of the drug development in the country of residence.

Recommendation for the route to deliver information/education material:

1, Medical Websites and Portals: Advertising on reputable medical websites and portals allows for targeted exposure to healthcare professionals and researchers.

2, Industry Conferences and Exhibitions: Participating in or sponsoring industry-specific conferences and exhibitions provides opportunities to highlight research and network with professionals in the field.

3, Pharmaceutical Magazines: Advertisements in pharmaceutical industry magazines can reach a broad audience of professionals involved in drug development. Free of charge magazines can also be distributed by Pharmacies using plain language to all audience.

4, Social Media Marketing: Utilizing platforms like LinkedIn and Twitter for targeted advertising helps connect with professionals, institutions, and organizations in the healthcare and pharmaceutical sectors.

5, Email Campaigns: Direct email campaigns targeting relevant professionals can provide detailed information about research progress, clinical trial updates, and potential collaborations.

6, Collaborations and Partnerships: Forming partnerships with other research institutions, pharmaceutical companies, or investors can increase visibility and support for drug development efforts.

7, Press Releases: Issuing well-crafted press releases can attract media attention and inform a wider audience about significant milestones or breakthroughs in drug research.

8, Educational Programs: Developing educational programs or webinars about the drug development process can engage professionals and non-professionals and raise awareness about specific research initiatives.

It is crucial to adhere to ethical guidelines and regulations when advertising drug research and development, ensuring that information is accurate, transparent, and complies with industry standards. The use of local language and appropriate level of phrasing should also be built in.

Recommended educational materials

Educating “laypeople” on general knowledge about clinical trials involves breaking down complex concepts into easily understandable information. Below you may find guide which can be adjusted and translated:

1, Define Clinical Trials:

Explain that clinical trials are research studies involving people that aim to evaluate new treatments, medications, or medical procedures.

2, Phases of Clinical Trials:

Describe the different phases (Phase I, II, III) and their purposes:

Phase I: Initial safety and dosage testing.

Phase II: Effectiveness and side effects evaluation.

Phase III: Large-scale testing for overall benefits and risks.

3, Informed Consent:

Emphasize the importance of informed consent, where participants are fully informed about the trial's purpose, procedures, potential risks, and benefits before deciding to participate. Also, important to point out that it is completely voluntary and can be withdrawn at any time.

4, Randomization and Control Groups:

Introduce the concepts of randomization and control groups, explaining how they contribute to unbiased and reliable results.

5, Blinding Process:

Explain blinding (single-blind or double-blind), where participants or researchers are unaware of the treatment assignment to minimize bias.

6, Placebo use in Clinical Trials:

Discuss the placebo effect and how it is considered in clinical trials to distinguish real treatment effects from psychological responses if applicable.

7, Patient Recruitment:

Describe how participants are recruited and the criteria used to ensure safety and relevance to the study.

8, Regulatory Oversight:

Highlight the role of regulatory bodies (such as the FDA, EMA, and National Authorities) in overseeing and approving clinical trials to ensure participant safety.

9, Duration of Trials:

Mention that clinical trials can take up to several years, from initial planning to the final analysis, emphasizing the commitment required.

10, Clinical Trial Results:

Clarify that results are shared with the scientific community and may contribute to advancements in medical knowledge and patient care.

11, Benefits and Risks:

Discuss the potential benefits for participants and society, as well as the importance of understanding and minimizing risks.

12, Real-life Examples:

Share real-life examples or success stories from clinical trials to make the information relatable. Patient Organizations can play a significant role in this process.

13, Accessible Resources:

Provide information on where “laypeople” can find reliable and accessible resources to learn more about clinical trials, such as government health or Regulatory Authorities websites or patient advocacy groups or patient organizations.

By presenting this information in a clear and accessible manner, one can help “laypeople” understand the significance of clinical trials in advancing medical knowledge and improving healthcare.

Conclusion

In conclusion, the exploration of clinical trial recruitment in this PhD dissertation has shed light on critical aspects of influencing the success and challenges within this pivotal phase of research. The findings underscore the multifaceted nature of recruitment, encompassing factors ranging from patient engagement to logistical considerations.

As we reflect on the culmination of this exploratory research, it becomes evident that effective education on drug development is essential for the recruitment willingness and timely completion of clinical trials and the generation of reliable results to deliver medicines to the world faster. The insights gained from analyzing responses and their outcomes provide a nuanced understanding of the complexities inherent in participant enrollment.

However, it is crucial to acknowledge the characteristic limitations and the evolving landscape of clinical trial recruitment. The ever-changing dynamics of healthcare, coupled with the diverse nature of study populations, necessitate continuous adaptation and innovation in recruitment approaches while the foundation should be the education of the population.

This exploratory research contributes to the existing body of knowledge by offering practical insights and recommendations to enhance recruitment processes. While it was aiming only the Hungarian population there is a strong possibility to implement to other Nations either.

The implications extend not only to the academic realm but also to the broader healthcare community, where improved recruitment practices can accelerate medical advancements and enhance patient outcomes.

As we move forward, it is my hope that the findings presented in this dissertation will stimulate further research and dialogue, fostering a collaborative effort to address the challenges and refine the strategies associated with clinical trial recruitment. Ultimately, by enhancing our understanding of this critical phase, we can collectively contribute to the advancement of medical research and the translation of innovative treatments from the laboratory to the bedside.

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IX. Appendices

Appendix 1

Questionnaire in Hungarian (Original)

Gyógyszerfejlesztés - Klinikai vizsgálatok

1. Kérem, adja meg a korcsoportját.

- ◯ 18-35 év
- ◯ 36-45 év
- ◯ 46-65 év
- ◯ 65 év felett

2. Neme

- ◯ Férfi
- ◯ Nő
- ◯ Egyéb

3. Iskolai végzettsége

- ◯ Általános iskola
- ◯ Középiskola (gimnázium, szakközépiskola, szakiskola)
- ◯ Felsőoktatási hallgató
- ◯ Főiskolai/Egyetemi diploma
- ◯ Posztgraduális képzés

4. Rendelkezik-e Ön egészségügyi végzettséggel?

- ◯ Igen
- ◯ Nem

5. Lakhely

- ◯ Főváros
- ◯ Nagyváros
- ◯ Kisváros
- ◯ Község
- ◯ Falu
- ◯ Tanya

6. Foglalkozás

- ◯ Nincs munkahely
- ◯ Tanuló
- ◯ Segédmunkás, betanított munkás
- ◯ Szakmunkás
- ◯ Irodai dolgozó
- ◯ Nem diplomás vezetői, irányítói munka
- ◯ Diplomás
- ◯ Diplomás vezetői munka

7. Van-e krónikus betegsége

- ◯ Nem
- ◯ Igen

8. Amennyiben van krónikus betegsége, melyik szervrendszert érinti

- ☐ Szív és érrendszer
- ☐ Mozgásszerv
- ☐ Légzőszerv
- ☐ Emésztőrendszer
- ☐ Vese
- ☐ Daganatos betegség
- ☐ Egyéb

9. Jár-e rendszeresen orvoshoz

- ◯ Igen
- ◯ Nem

10. Havi nettó jövedelme

- ◯ 50.000 - 100.000 Ft
- ◯ 100.001 - 300.000 Ft
- ◯ 300.001 - 500.000 Ft
- ◯ 500.001 - 700.000 Ft
- ◯ több, mint 700.000 Ft

11. Családi állapota

- ◯ Kapcsolatban él
- ◯ Családos
- ◯ Egyedülálló

12. A lehetőségeimhez mérten egészségtudatos vagyok

	0	1	2	3	4	5	6
0 egyáltalán nem, 6 teljes mértékben	◯	◯	◯	◯	◯	◯	◯

13. Megfelelő ismerettel rendelkezem az egészséges életmóddal illetve az egészségügyi lehetőségeimmel kapcsolatban.

	0	1	2	3	4	5	6
0 egyáltalán nem, 6 teljes mértékben	◯	◯	◯	◯	◯	◯	◯

14. Megfelelő ismerettel rendelkezem a gyógyszerekkel kapcsolatban

	0	1	2	3	4	5	6
0 egyáltalán nem, 6 teljes mértékben	◯	◯	◯	◯	◯	◯	◯

15. Megfelelő ismerettel rendelkezem a gyógyszerkutatás-fejlesztéssel kapcsolatban

	0	1	2	3	4	5	6
0 egyáltalán nem, 6 teljes mértékben	◯	◯	◯	◯	◯	◯	◯

16. Megfelelő ismerettel rendelkezem a gyógyszeres klinikai kutatásokkal kapcsolatban

	0	1	2	3	4	5	6
0 egyáltalán nem, 6 teljes mértékben	◯	◯	◯	◯	◯	◯	◯

17. Ön szerint mennyire hasznosak a gyógyszeres klinikai vizsgálatok a társadalom számára

	0	1	2	3	4	5	6
0 egyáltalán nem, 6 teljes mértékben	◯	◯	◯	◯	◯	◯	◯

18. Vett-e már részt gyógyszeres klinikai vizsgálatban?

◯ Igen

◯ Nem

19. Mennyire valószínű, hogy részt venne gyógyszeres klinikai vizsgálatban?

	0	1	2	3	4	5	6
0 egyáltalán nem, 6 teljes mértékben	◯	◯	◯	◯	◯	◯	◯

20. Ha nem venne részt gyógyszeres klinikai vizsgálatban, mik a fő okok az alábbiak közül? Kérem, rangsorolja

- Nem kellő ismeret
- Bizalom hiánya
- Időhiány
- Félelem

21. Ha Ön beteg/megbetegedne és orvosa felajánlaná a részvételt gyógyszeres klinikai vizsgálatban, mennyire valószínű, hogy részt venne?

	0	1	2	3	4	5	6
0 egyáltalán nem, 6 teljes mértékben	◯	◯	◯	◯	◯	◯	◯

22. Ha Ön beteg/megbetegedne és orvosa felajánlaná a részvételt gyógyszeres klinikai vizsgálatban, kivel beszélné meg?

- [ ] Vizsgálatot vezető orvos
- [ ] Háziorvos
- [ ] Család
- [ ] Ismeretségi kör
- [ ] Egyéb

23. Ön szerint mik azok a faktorok, amik gyógyszeres klinikai kutatásban való részvétel mellett szólnak?

- [ ] Orvos-beteg kapcsolat
- [ ] Saját ismeret
- [ ] Család véleménye
- [ ] Barátok véleménye
- [ ] Gyógyszercég ismertsége
- [ ] Egyéb

24. Ön szerint miért vesznek részt betegek gyógyszeres klinikai vizsgálatban?

- [ ] Egyéni felelősségvállalás
- [ ] Kíváncsiság
- [ ] Jobb orvosi ellátás
- [ ] Modernebb kezeléshez való hozzáférés
- [ ] Gyógyszerekbe vetett bizalom
- [ ] Társadalmi felelősségvállalás
- [ ] Egyéb

25. Ön szerint miért vesznek részt egészséges önkéntesek gyógyszeres klinikai vizsgálatban?

- [ ] Egyéni felelősségvállalás
- [ ] Kíváncsiság
- [ ] Gyógyszerbe vetett bizalom
- [ ] Gyógyszergyártóba vetett bizalom
- [ ] Társadalmi felelősségvállalás
- [ ] Pénz
- [ ] Egyéb

26. Ha Ön részt venne gyógyszeres klinikai vizsgálatban EGÉSZSÉGES ÖNKÉNTESKÉNT, mik lennének a fő okok?

- [ ] Egyéni felelősségvállalás
- [ ] Kíváncsiság
- [ ] Gyógyszerbe vetett bizalom
- [ ] Gyógyszergyártóba vetett bizalom
- [ ] Társadalmi felelősségvállalás
- [ ] Jobb orvosi ellátás
- [ ] Pénz
- [ ] Egyéb

27. Ha Ön részt venne gyógyszeres klinikai vizsgálatban BETEGKÉNT, mik lennének a fő okok?

- [ ] Egyéni felelősségvállalás
- [ ] Kíváncsiság
- [ ] Gyógyszerbe vetett bizalom
- [ ] Gyógyszergyártóba vetett bizalom
- [ ] Társadalmi felelősségvállalás
- [ ] Jobb orvosi ellátás
- [ ] Egyéb

28. Ha felkérnék Önt, hogy csatlakozzon egy gyógyszeres klinikai vizsgálathoz, hogyan tájékozódna a döntése előtt?

- [ ] Vizsgálatvezető orvosa
- [ ] Háziorvosa
- [ ] Egészségügyi dolgozók
- [ ] Barátok, család, ismerősök
- [ ] Internet
- [ ] Betegszervezetek
- [ ] Rádió
- [ ] Televízió
- [ ] Gyógyszercégek honlapja
- [ ] Gyógyszerhatóság honlapja
- [ ] Egyéb

29. Ön miről hallana/olvasna legszívesebben a gyógyszerkutatás-fejlesztésről

- [ ] Általános ismeretek a gyógyszerkutatás-fejlesztésről
- [ ] Klinikai vizsgálatok fázisai
- [ ] Gyógyszerkutatás-fejlesztés helyzete az Ön országában
- [ ] Gyógyszerkutatás-fejlesztés jogi-etikai háttere, szabályozása
- [ ] Hol tájékozódhat futó klinikai vizsgálatokról
- [ ] Egyéb

30. Kérem, rangsorolja a klinikai vizsgálatokkal kapcsolatos információforrásokat megbízhatóságuk szerint.

- Vizsgálatvezető orvos
- Háziorvos
- Internet
- Rádió
- Televízió
- Írott sajtó
- Nyomtatványok, szórólapok
- Betegszervezetek
- Gyógyszerhatóság honlapja
- Gyógyszercégek honlapja

Appendix 2

Questionnaire in English (translation not validated)

Drug Development – Clinical Trials

1. Please indicate your age group.

- ◯ 18-35 years
- ◯ 36-45 years
- ◯ 46-65 years
- ◯ above 65 years

2. Gender

- ◯ Male
- ◯ Female
- ◯ Other

3. Please indicate your highest qualification

- ◯ Elementary School
- ◯ High School
- ◯ College/University Student
- ◯ College/University Diploma
- ◯ Postgraduate Diploma

4. Do you have any Healthcare Degree?

- ◯ Yes
- ◯ No

5. Please indicate your habitation

- ◯ Capital
- ◯ City
- ◯ Town
- ◯ Parish
- ◯ Village
- ◯ Farm

6. Please indicate your occupation

- ◯ No occupation
- ◯ Student
- ◯ Unskilled worker
- ◯ Skilled workman
- ◯ Office worker
- ◯ Leader without diploma
- ◯ Diploma
- ◯ Leader with diploma

7. Do you have chronic disease?

- ◯ No
- ◯ Yes

8. If yes which organ is affected?

- ☐ Circulatory system
- ☐ Locomotor system
- ☐ Respiratory system
- ☐ Digestive system
- ☐ Kidney
- ☐ Oncology disease
- ☐ Other:

9. Have you visit physician regularly?

- ◯ Yes
- ◯ No

10. Your monthly net wage:

- ◯ 50.000 - 100.000 HUF
- ◯ 100.001 - 300.000 HUF
- ◯ 300.001 - 500.000 HUF
- ◯ 500.001 - 700.000 HUF
- ◯ more than 700.000 HUF

11. Marital status

- ◯ In relationship
- ◯ Married
- ◯ Single

12. According to my possibilities I am health-conscious

	0	1	2	3	4	5	6
0 not at all, 6 absolutely	◯	◯	◯	◯	◯	◯	◯

13. I have ample knowledge concerning healthy lifestyle and my healthcare possibilities.

	0	1	2	3	4	5	6
0 not at all, 6 absolutely	◯	◯	◯	◯	◯	◯	◯

14. I have ample knowledge concerning medications

	0	1	2	3	4	5	6
0 not at all, 6 absolutely	◯	◯	◯	◯	◯	◯	◯

15. I have ample knowledge concerning drug development

	0	1	2	3	4	5	6
0 not at all, 6 absolutely	◯	◯	◯	◯	◯	◯	◯

16. I have ample knowledge concerning clinical trials

	0	1	2	3	4	5	6
0 not at all, 6 absolutely	◯	◯	◯	◯	◯	◯	◯

17. According to your opinion how useful the clinical trials are to the society?

	0	1	2	3	4	5	6
0 not at all, 6 absolutely	◯	◯	◯	◯	◯	◯	◯

18. Have you ever participated in clinical trials?

◯ Yes

◯ No

19. How likely you would participate in clinical trial?

	0	1	2	3	4	5	6
0 not at all, 6 absolutely	◯	◯	◯	◯	◯	◯	◯

20. If you would not participate in clinical trial what would be the main factors? Please rank it.

- Inadequate knowledge
- Lack of thrust
- Lack of time
- Fear

21. If you ill or became ill, and your Physician offered you to participate in a clinical trial how likely you would participate?

	0	1	2	3	4	5	6
0 not at all, 6 absolutely	◯	◯	◯	◯	◯	◯	◯

22. If you ill or became ill, and your Physician offered you to participate in a clinical trial to whom you may consult?

- [ ] Principal Investigator
- [ ] Family doctor
- [ ] Family
- [ ] Acquaintanceship
- [ ] Other:

23. According to your opinion which factors are in favor to participate in clinical trial?

- [ ] Physician-patient relationship
- [ ] Own knowledge
- [ ] Family's opinion
- [ ] Friends' opinion
- [ ] Reputation of Pharmaceutical Company
- [ ] Other:

24. According to your opinion why patients are participating in clinical trials?

- [ ] Personal responsibility
- [ ] Curiosity
- [ ] Better medical care
- [ ] Access to modern treatment possibilities
- [ ] Thrust in medicines
- [ ] Social responsibility
- [ ] Other:

25. According to your opinion why healthy volunteers are participating in clinical trials?

- [ ] Personal responsibility
- [ ] Curiosity
- [ ] Thrust in medicines
- [ ] Trust in Pharmaceutical Company
- [ ] Social responsibility
- [ ] Money
- [ ] Other:

26. If you would participate in a Clinical Trial as HEALTHY VOLUNTEER what would be the main factors?

- [ ] Personal responsibility
- [ ] Curiosity
- [ ] Thrust in medicines
- [ ] Thrust in Pharmaceutical Company
- [ ] Social responsibility
- [ ] Better medical care
- [ ] Money
- [ ] Other:

27. If you would participate in a Clinical Trial as PATIENT what would be the main factors?

- [ ] Personal responsibility
- [ ] Curiosity
- [ ] Thrust in medicines
- [ ] Thrust in Pharmaceutical Company
- [ ] Social responsibility
- [ ] Better medical care
- [ ] Other

28. If you were asked to participate in a Clinical Trial how you would you get information before your decision?

- [ ] Principal Investigator
- [ ] Family doctor
- [ ] Healthcare professionals
- [ ] Acquaintanceship
- [ ] Internet
- [ ] Patient Organization
- [ ] Radio
- [ ] TV
- [ ] Pharmaceutical Company's web page
- [ ] Regulatory Authority's web page
- [ ] Other

29. What would you read/hear the most concerning drug research and development?

- [ ] General information on drug Research and Development
- [ ] Phases of Clinical Trials
- [ ] General status of drug Research and Development in your Country
- [ ] Legal and ethical background of drug Research and Development
- [ ] Where can I find information on currently ongoing Clinical Trials
- [ ] Other

30. Please rank the source of information concerning Clinical Trials according to the level of trustworthiness

- Principal Investigator
- Family doctor
- Internet
- Radio
- TV
- Printed media
- Sheets, flyers
- Patient Organizations
- Regulatory Authority website
- Pharmaceutical Companies website

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