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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Στρατηγικές ψηφιακού μάρκετινγκ για τη διεξαγωγή κλινικών δοκιμών με στόχο την εξοικονόμηση χρόνου και τη μείωση κόστους για τη φαρμακευτική έρευνα

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INTERISTITUTIONAL PROGRAM OF POSTGRADUATE STUDIES IN BIOENTREPRENEURSHIP

MASTER THESIS

Digital Strategies in Clinical Trials

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Vasiliki Papanikolaou
A.M. 00035
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Η παρούσα διπλωματική εργασία εκπονήθηκε στο πλαίσιο σπουδών για την απόκτηση του Μεταπτυχιακού Διπλώματος Ειδίκευσης στο

ΒΙΟΕΠΙΧΕΙΡΕΙΝ

που απονέμει το Τμήμα Βιοχημείας και Βιοτεχνολογίας του Πανεπιστημίου Θεσσαλίας, σε συνεργασία με *χώρος εκπόνησης της διπλωματικής εργασίας* (αν υπάρχει).

Εγκρίθηκε την …….. από την τριμελή εξεταστική επιτροπή:

ΤΡΙΜΕΛΗΣ ΕΠΙΤΡΟΠΗ

ΟΝΟΜΑΤΕΠΩΝΥΜΟ	**ΒΑΘΜΙΔΑ**	**ΥΠΟΓΡΑΦΗ**
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I would like to thank Dr. Zervou for her trust on letting me choose the objective of this thesis.

I am grateful to have her constant support and her valuable guidance during this time.

To my family and especially to my grandmother Aikaterini.

Contents

Abstract

The aim of this thesis is to present how digital marketing and innovative strategies can empower and amplify the clinical research in order to gain both economic and therapeutic value in the drug development process.

Clinical trials are undoubtedly the backbone in pharmaceutical research and their outcomes are crucial to the patients as well as to all concerned stakeholders; hence, there are numerous reasons and considerable pressure to optimize them. (Gupta, 2012)
This dissertation is structured in seven chapters, describing and documenting the drug development processes, analyzing the major barriers, highlighting the significance of clinical research and evaluating the role of digital marketing in study participants' awareness.
In the first and second chapter of this thesis, introduction and drug development process are presented. Subsequently, in chapter 3, the Barriers and Costs for conducting clinical research are extensively analyzed, covering also the limited patients' awareness about clinical trials. Patients' awareness and perceptions of clinical trials, as well as attitudes of physicians, are some of the main restrictions, underlying the low recruitment rate.
Moving forward on the next chapter, the role of Marketing and the significant contribution of digital marketing are presented, in an attempt to describe the affect and the powerful connection with health sciences. The importance of high recruitment rate in clinical trial is assessed as well as digital means to invest on a successful clinical study. The regulations framework is analytically described in chapter 5, where all clinical studies are managed and controlled.
In the sixth chapter a new approach aiming to encourage greater participation in the clinical trials is presented. Particularly, the designed case study combines an awareness campaign involving important stakeholders. The presented study is supported by google ads towards the creation of new a user-friendly webpage (www.BEpartofthefuture.com), targeting the increase of the recruitment rate in clinical research.
Finally, in chapter 7 general thoughts and concerns about the future of clinical research are summarized, presenting also potential ideas and innovative strategies.

Keywords

Clinical Research, Marketing, Digital era, Campaign, Regulations, R&D, Innovation

The scope

The main purpose of the present thesis is to assess the existing knowledge about clinical trials and analyze innovative marketing strategies, aiming to find an innovative way to improve the quality and the benefits of clinical trials.

The discovery and development of new drugs is a very lengthy and costly process. The pharmaceutical companies are constantly targeting to improve both their services in health system and trials efficiency as well as to decrease the costs.
Undoubtedly, the increasing costs of clinical research have significant implications on public health, as it affects drug companies' willingness to undertake clinical trials, resulting in fewer ''novel"[i] treatments. Moreover, drug failures are key contributors to development costs. It is also shown that lack of recruitment is one of the major factors leading the clinical trials to be unsuccessful. It is widely known that dedicated participation is an essential aspect of a successful completed clinical trial, but the optimal methods of improving recruitment to clinical research is yet to be studied.
One of the key factors for successful recruitment is patients' awareness and willingness to participate in potential clinical studies. Patients can make informed decisions about their health only if they are able to access all the relevant information, in an easily understandable way.

Designing an awareness campaign, by adjusting new digital ideas and using tools like google ads could allow a pharmaceutical company to eliminate the likelihood of trial failure, saving time and billions for the company and ensure that people can have access to the live-saving new treatments.

Abbreviations

CRO	Clinical Research Organization
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EOF	National Organization for Medicines
FDA	U.S Food and Drug Administration
GCP	Good Clinical Practices
ICF	Inform Consent Form
IRB	Institutional Review Board
NDA	New Drug Application
PASS	Post Authorization Safety Studies

Figures and Tables

1. INTRODUCTION

One of the main concerns of pharmaceutical companies nowadays is that their expenses have grown faster than other major components of the health care system since the late 90s. Due to the rising health care costs in the pharma industry, it is essential that companies develop and implement innovative tactics that will help them address this issue. (M.Ding, 2014).

It is beyond doubt that innovations in the scientific world have resulted in dramatic changes in the way that diseases are treated nowadays, improving daily and constantly the quality of life while also contributing positively to the reduction of the costs. (M.Ding, 2014)

Although the industry engages in many ways in innovation, the most significant one is the discovery and development of new chemical and biopharmaceutical entities that become new therapies. In the research-based drug industry, R&D decisions have very long-term ramifications, that may not be fully realized for years. It is therefore essential that companies continue analyzing the trends and components of costs of pharmaceutical innovation.

It is also commonly known that companies that are strong in both innovation and marketing can create value and billion of dollars for their stakeholders.[1](M, 2015) In the process of finding effective structures and efficient strategies that foster innovation, new opportunities and challenges constantly arise and therefore new organizational forms and arrangements emerge to address them.

In conjunction with innovation, the increased use of the Internet and other digital media has also enabled the collection of information for physicians, patients, and other stakeholders.

Last but not least, it goes without saying that digital communication is a powerful tool that can be used by companies in their integrated marketing communication campaigns since it allows them to interact in an informal and more personal way.

[1] (M, 2015)

Figure 1 Innovation and Marketing [2]

2. Clinical trials in drug development

2.1 Historical Background

Before WWII, the relations between the pharmaceutical industry and the life sciences were relatively tenuous. Most new drugs were derived from natural sources (herbs) or were based on existing compounds, mostly of organic origin. Little formal testing was done to ensure their safety or efficacy. [3] (Drager N, 2001)

During World War II, Nazi doctors conducted '' experiments'' on concentration prisoners. These atrocities performed without the consent of the inmates. Immediately after the war, in August 1947 the Nuremberg code was created, as a result of the Nuremberg medical trials. This code is accepted worldwide and recognizes that the risk must be weighed against the expected benefit.[4] (Utley, 1992)

[2] (M.Ding, 2014)
[3] (Drager N, 2001)
[4] (Utley, 1992)

In 1964, the Declaration of Helsinki was developed by the World Medical Association, forming the basis for the ethical principles that underlie the ICH-GCP (International Conference on Harmonization-Good Clinical Practice) guidelines we have today.[5] (Evelyne Shuster, 1997)

The World Medical Association (WMA) combined the Nuremberg code with the Declaration of Geneva, setting the ethical guidelines for physicians and other participants in medical research. (Drager N, 2001)

In 1972, news reports revealed flagrant misconduct in the Tuskegee study, which was conducted by the U.S. government. This experiment began on 1932 and ended on 1972 with the promise of medical care to 600 poorly educated African American men, 399 with syphilis, 201 who did not have the disease. The men with syphilis were never administered adequate treatment for their disease, even though penicillin became the drug of choice for syphilis in **1947.** [6] [7]

The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men,

Figure 2 New York Times article for Tuskegee Study [8]

[5] (Evelyne Shuster, 1997)
[6] https://www.cdc.gov/tuskegee/timeline.htm
[7] (Americans' views on research and the Tuskegee Syphilis Study, 2001)
[8] https://www.asbmb.org

Following this study, the US government proceeded on new federal regulations, changing their research practice and establishing the Health and Human Services Policy preventing a repeat of these inhumanities. As a result, all research involving human subjects must now be reviewed and approved by an Institutional Review Board (IRB). These federal regulations set the basis for oversight of clinical trials today. (M.Ding, 2014)

2.2 Pharmaceutical Industry

Despite of the great contribution of academic laboratories in the life sciences and medicine, and in the development of many pharmaceutical compounds, most new therapies were developed by pharmaceutical companies.[9]

The pharmaceutical industry based its strategies on the primary goal of improving the quality of life. For this reason, regulations and all related parties (doctors, pharmacists, government) are designated to protect the patient's wellbeing at reasonable cost.
It is the only industry focused on relieving the physical pain thus, pharmaceutical companies are under such tremendous pressures to innovate.
The research pharmaceutical firms bring the new molecules and medicines to the market. This is an expensive, long and complex process involving extremely risks and strict regulations.
It is referred that pharmaceutical industry consistently grows 4–7 %per year. The successful and rapid launch of new therapies is the way to accelerate growth. (M.Ding, 2014)

2.3 Clinical Trials

Clinical trials are medical research studies involving people and the outcomes are being used as important supportive information for researchers and doctors, and in the end for patients.
These aim to find out if a new treatment is safe, presents any side effects and offers better remission than the existing treatment.
It is known that clinical trials are complex as the participation and collaboration by many parts, like patients, physicians, government etc. is crucial. Limited engagement of these

[9] (Basil Achilladelis, 2000)

stakeholders can drive in study failures. [10]

According to the National Institutes of Health (NIH), a clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. (J.Deans, 2018)

Their outcome can be used to generate data on safety, efficacy, and/or effectiveness of treatments. They are designed to test a pre-specified hypothesis and enroll a pre-specified number of patients needed to have enough statistical power to detect the proposed treatment difference. [11](J.Deans, 2018)

Clinical trials can be classified in several ways. Particularly, the NIH organizes clinical trials into five different types based on their purpose.
These include:

- Prevention trials which investigate how to prevent disease or disease recurrence
- Screening trials which focus on ways to detect certain diseases or health conditions
- Diagnostic trials which examine tests/procedures for diagnosing a disease
- Treatment trials which compare experimental or established treatments including drugs, devices, or procedures
- Quality of life trials which investigate therapies or interventions to improve the comfort and quality of life for patients with chronic illnesses.

The development of a drug is typically a long process that lasts several years. Drugs are often tested in humans only after they have undergone preclinical laboratory testing. Subsequently, there are several phases and stages of approval in the clinical trials process before a drug or device can be sold in the consumer market, if ever. Human Clinical Trial phases are usually conducted in four phases.
Each phase has a different purpose and design, using the results from the previous phase to develop the next.
Phase I trials assess the safety of a drug or device. It involves the evaluation of pharmacokinetic parameters and tolerance, generally in a small sample size (10-80 healthy volunteers). The first step of clinical studies is about to gather the initial information and answer biological questions as pharmacodynamics of different doses of the investigational drug.

[10] (A. Mahmud, 2018)
[11] (J.Deans, 2018)

Phase II are small-scale clinical studies evaluating the treatment's safety and efficacy. Phase II trials start once the initial safety of the drug has been established. They can last from several months to two years and usually involve a larger sample size (100- 300 patients). When the efficacy and safety of the drug have been checked for the disease or condition under investigation, drug development will proceed to phase III.

Phase III studies attempt to verify a study drug's efficacy against the current standard treatments.

These large-scale trilas, which can last several years, provide the pharmaceutical company and the FDA with a more thorough understanding of the effectiveness of the drug or device, the benefits and the range of possible adverse effects.

Due to the large sample size (500 to 3000 patients), often the multi-institutional collaborations are required and can take many years to complete. The phase III trial provides the necessary information for assessing whether the drug can be approved and licensed.

While phase III studies are in progress, preparations are made for submitting the Biologics License Application (BLA) or the New Drug Application (NDA). BLAs are currently reviewed by the FDA's Center for Biologics Evaluation and Research (CBER) while NDAs are reviewed by the Center for Drug Evaluation and Research (CDER).

Phase IV trials are performed after a new treatment has received FDA approval. These post-market trials take place once the drug has been licensed for marketing based on the results of a phase III trial.[12] [13] (J.Deans, 2018) [14]

Clinical trials can also be classified as either "fixed" or "adaptive" based on whether the trial design allows for changes as data is collected during the trial. Most clinical trials are fixed trials. These trials only consider existing data during the initial design, do not allow modifications once the trial has begun, and only assess the results at completion of the trial.[15] (Gupta R. M., 2010)

In contrast, adaptive clinical trials use existing data to design the trial, and then use interim results to modify the trial as it proceeds. The adaptive design allows modifications made to trial and/or statistical procedures of ongoing clinical trials.

Adaptive methods based on accrued data has become very popular due to its flexibility and efficiency.

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[12] https://pacificbiolabs.com/stages-of-drug-development#clinical
[13] (Prayle, 2012)
[14] (Philip Sedgwick, 2011)
[15] (Gupta R. M., 2010)

Adaptive model is very attractive to researchers because it reflects medical practice in real world. It is flexible to stop early the trial if there are safety reasons or efficacy. Also, the sample size can re-estimate if needed at interim for achieving the appropriate statistical power. [16] (Gupta R. M., 2010)

Bayesian design provide a mathematical method for combining prior information with current information at the design stage, during the conduct of the trial, and at the analysis stage.
A Bayesian statistics design is usually adjusted on adaptive trials planning of more quickly identifying beneficial treatment effects of an intervention and identifying specific populations for whom the intervention is beneficial.
It also provides an efficient and effective method for evaluating new medication during the early phases of drug development.
The roots of Bayesian statistics lie in Bayes' theorem related to the increase of the precision of the information from a current trial by the incorporation of prior information.
Any change in the prior information at a later stage of the trial may hamper the scientific validity of the trial results. (Chang, 2008) (Gupta, 2012)

Blinding (sometimes called masking) is used to try to eliminate any potential bias.
In blinded clinical trials the treatment allocation for each patient is not revealed until the patient has irrevocably been entered the trial, to avoid selection bias. In controlled trials the term blinding, and in particular "double blind," usually refers to keeping study participants, those involved with their management (investigators, study team), and those collecting and analyzing clinical data (sponsor, company) unaware of the assigned treatment, so that they should not be influenced by this information.
The major advantage of these trials is that in a double-blind trial the assessment of patient outcome is done in ignorance of the treatment received. (Chang, 2008)

Randomized controlled trials are the gold standard of medical research. Randomization minimizes the possibility of selection bias, and it tends to balance the treatment groups over variables. (Chang, 2008)
In a Randomized Clinical Trials (RCTs) two or more groups of patients are randomized and compared: They can be enrolled on the experimental group who receive a new study drug or on a control group where patients receive the current standard treatment or placebo. In clinical trials, placebo is generally the control treatment with a similar appearance and

[16] (Chang, 2008)

structure to the study treatment but without its specific activity. [17](Asbjørn Hróbjartsson, 2001)

Nowadays, Randomized Clinical Trials (RCTs) are frequently used but they have several limitations. First, they are difficult to perform because they require significant financial resources for study staff, treatment interventions, data collection, monitoring, and analyses.

It is known that recruitment to randomized controlled trials can be very challenging.

The shortage of patients may require a large multi-institutional effort, increasingly importantly the cost. (Chang, 2008)

All clinical trials should be designed and conducted under the GCP Guidelines assuring the rights, safety and well-being of trial subjects.

Good Clinical Practice (GCP) is an international ethical and scientific standard for conducting biomedical and behavioral research involving the participation of human subjects. [18]

2.4 Drug Development Process

Under FDA requirements, a sponsor must first submit data (preclinical data) showing that the drug is reasonably safe for use in initial, small-scale clinical studies.

Before any human subjects can be enrolled in the clinical studies, a safe starting dose must be established.

This can be succeeded with preclinical studies, evaluating the desired biological effect of a drug in order to predict treatment outcome in patients (efficacy) and to characterize all toxicities associated with a drug in order to anticipate potential adverse events in people (safety).

The use of animal models has been essential to achieving the preclinical studies as well as understanding a numerous medically unexplained disease. Animal models have been used to provide the preliminary safety and efficacy testing for nearly all therapeutics in use today. [19]

Upon completion of drug discovery and preclinical studies, the pharmaceutical company prepares for the next critical stage in the innovation process—drug development through

[17](Asbjørn Hróbjartsson, 2001)
[18] (Group, 1996)
[19] (Choosing the right animal model for infectious disease researchConsiderations for Infectious Disease Research Studies Using Animals, 2018)

clinical trials on humans. Before clinical trials can begin, the researchers must submit an Investigational New Drug (IND) application to the FDA. [20]

As part of the submission, the drug sponsor must provide all clinical evidence such as Certification of Compliance, Statement of Compliance etc. in support of **claims about** the primary drug indication (the targeted medical condition).

Thirty days after a biopharmaceutical company has filed its IND, it may begin a small-scale Phase I clinical trial unless the FDA places a hold on the study.

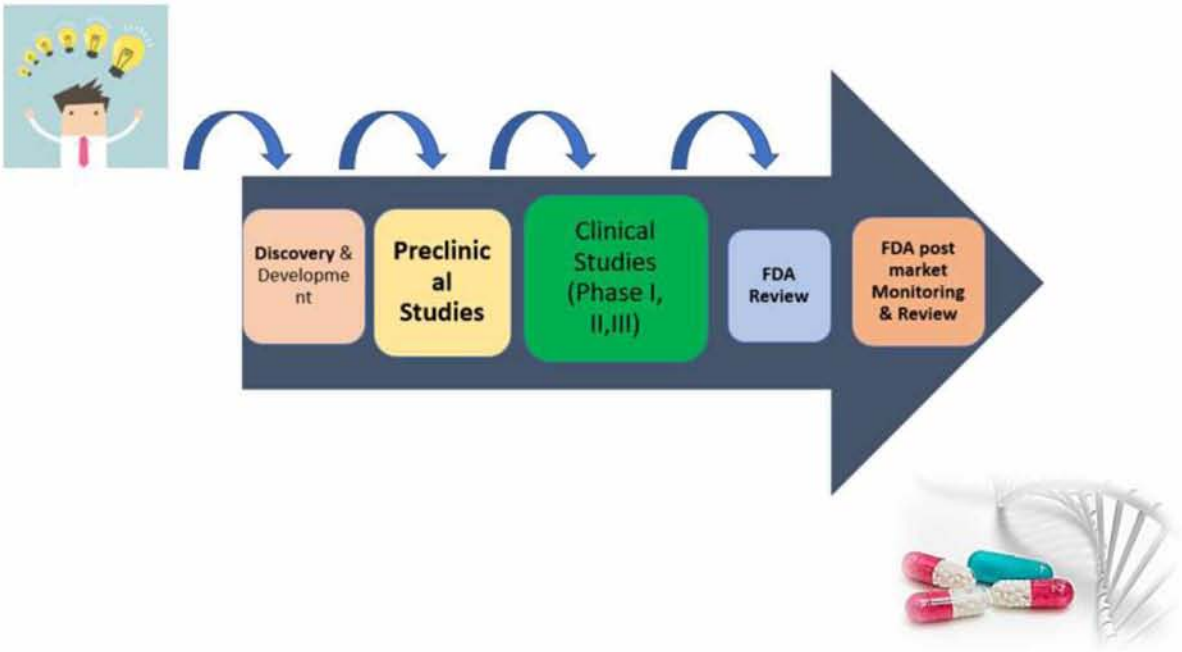

Figure 3 Drug Development Stages

2.5 The interested parties

Investigators: The Principal Investigator bears responsibility for the conduct of the trial at the investigational site ensuring the proper and compliant performance of the clinical research.

The Principal Investigator must be **qualified** by education, training and experience to assume responsibility for the ethical conduct of the trial. Trial-related procedures, medical care and medical decisions must be made by a physician who is the PI or a sub-investigator.

[20] https://pacificbiolabs.com/stages-of-drug-development#clinical

Regulatory Authorities: **The European Medicines Agency (EMA) is the** European Union agency for the evaluation and supervision of medical products and **The Food and Drug Administration (FDA)** is a Federal agency of the US Department of Health and Human Services with scientific, regulatory and public health responsibilities. These organizations are responsible for protecting the public health by assuring the safety, efficacy of human new treatments.

Moreover, FDA and EMA are designated to foster the research innovation with advanced medicines, more effective, safer and more affordable, improving human being life.[21] [22]

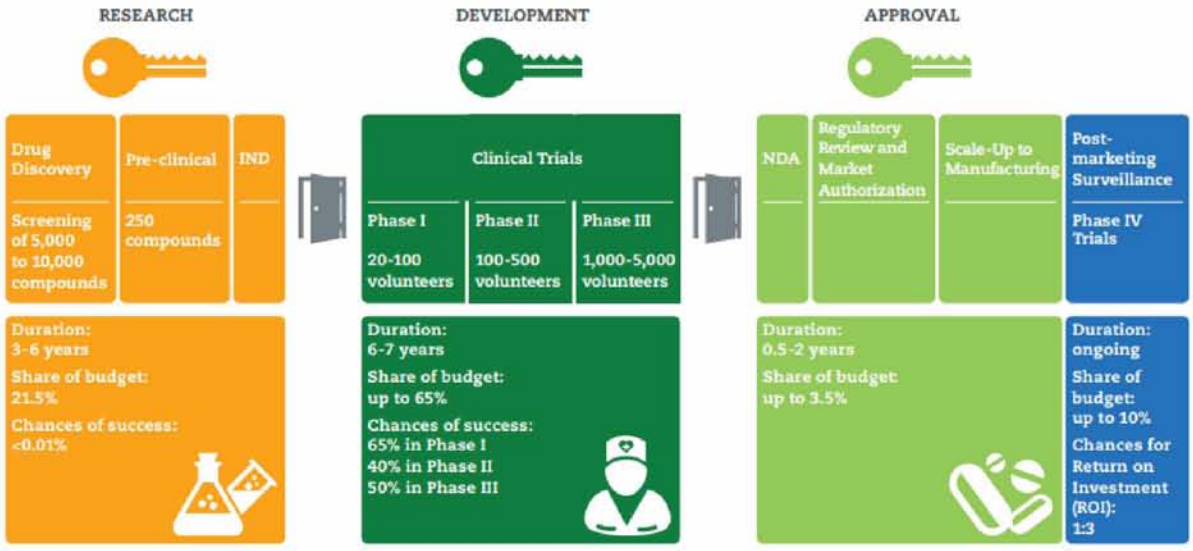

Figure 4 The Research and Development Process[23]

National Regulatory Authorities: Clinical research cannot be done without the support of the national authorities.

The involvement of an independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members is vital.

Their responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in

[21] https://www.ema.europa.eu/en
[22] https://www.fda.gov/
[23] (Associations, 2017)

obtaining and documenting informed consent of the trial subjects
For Greece, the competent authority is EOF and NEC (National Ethics Committee) who are important part of studies completion, coordinating and controlling all study procedures under specific regulations and laws. [24]

Sponsor: The sponsor is responsible to manage and preserve the quality throughout all stages of the trial process.
The sponsor can be an individual, a company, an institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
Sponsors also should ensure human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making.
The sponsor should identify risks in system level (Standard Operating procedures, etc) as well as in clinical trial level (trial design, data collection etc).
Regardless, industry is a major player in clinical research because in short, they have the molecules and they handle the budgets. [25]

3. Barriers in New Drug Development

3.1 R&D Costs and time for the pharmaceutical company

Pharmaceutical and biopharmaceutical companies confront with a host of challenging barriers in their quest to bring innovative new medicines to market.
Drug development is a complex, laborious, time consuming, and costly process with very uncertain outcomes. Even if the initial screening and testing have shown propitious indications, the chances of a promising drug candidate to make it through the sequential stages of the drug development process remain around one in five (20%).
Pharmaceutical firms are under growing pressure from a range of environmental issues, political changes, patents expirations, increasingly cost-constrained healthcare systems and more demanding regulatory requirements. The challenge for policymakers, acknowledging

[24] https://www.eof.gr/web/guest/law
[25] https://ichgcp.net/5-sponsor/

that health care budgets are limited, is to balance access for new medicines while providing the right incentives to industry. [26]

Figure 5 Pharmaceutical R&D expenditure in Europe, USA and Japan the period 1990-2016 [27]

Healthcare budgets are limited, so the profitability and growth prospects are also under pressure. It is referred that the average cost of developing a successful new drug has surpassed US$1B, increasing from an estimate of US$360M in the mid-1990s. This increase reflects the various technical, regulatory and economic challenges facing R&D pipelines. (M.Ding, 2014)

An overall clinical approval success rate is the probability that a compound that enters the clinical testing pipeline will eventually be approved for human use. **Attrition rates** describe the rate at which investigational drugs fall out of testing in the various clinical stages.

In pharmaceutical companies the failed-rejected projects are also counted in the total cost. It is mentioned that 1 in 10 new drug projects succeed but the total cost of developing one successful drug includes the cost as well of the 9 failed projects.

Additionally, **time** is a major factor in drug development process, as can often determine the

[26] (DiMasi, 2003)
[27] https://www.efpia.eu

success. For that, it is necessary to know at what stage of clinical development expenditures occur. Drug development takes more time than in the past. Studies have shown that the average clinical development time for drugs approved between 2005 and 2009 was 6.4 years while newer data showed that the composite median interval duration for ongoing development projects (2008–2012) is 9.1 years. [28]

R&D costs have increased rapidly over the last 10 years, only a small percentage of drugs in the R&D stage receive finally the approval from regulators.
High R&D costs reflect the tremendous challenge of developing products for ever more chronic and complex diseases, for example, neurodegenerative and oncology indications.
Tufts Center for the Study of Drug Development data showed that the average time to bring a new pharmaceutical product to market, from the start of clinical testing to FDA approval, is 8.5 years, and the clinical success rate is 21.5%. It is worth noting that in the neurogenerative area those figures are 10.8 years and 14% and in the oncology area they are 9.3 years and 8%. (M.Ding, 2014)

According to PhRMA (Pharmaceutical Research and Manufacturers of America 2010), on average, **53.6** % of the **innovation cost** is spent on clinical trials. [29]

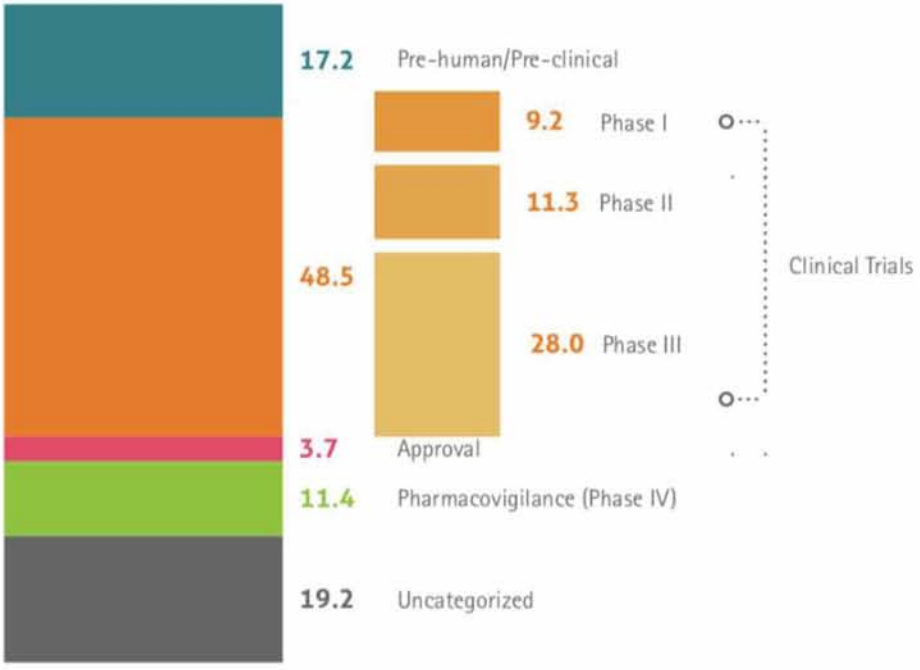

Figure 6 PhRMA, Annual Membership Survey 2017

[28] (Alexander Schuhmacher, 2016)
[29] https://www.phrma.org/

3.2 Generic drugs

When the patent on a drug expires, generic drugs can enter the market.
These have substantially lower prices than the branded drug before patent expiry and take a large share of the market. It leads to drastic changes in the average price of a molecule as inexpensive generics enter and the demand for the branded drug largely shifts to generics.

At 2018, generic drugs account for more than 88% of drugs prescribed while on prior to 1984 was only 19%. Since R&D and general expenses are importantly lower than branded drugs, biosimilars can be sold at a much lower price.[30]

3.3 Clinical Trials and Low recruitment

Preclinical (discovery and preclinical development) costs also grew in real terms, but much more slowly than in the past. The widespread use of discovery technologies, such as combinatorial chemistry techniques and high-throughput screening, may have succeeded to reduce the preclinical costs. However, undoubtedly the preclinical studies' costs are substantial. [31]
Also, the clinical success is estimated at less than 12% by the Pharmaceutical Research and Manufacturers of America (PhRMA). This leads to one of the key issues, the high cost of failure. Only 32% of drugs make it to Phase III clinical studies, and a mere 10% go to market. As a result, companies may lose between $800 million to $1.4 billion. Shareholders also suffer major losses, but even more significantly, patients lose out on potentially life-saving treatments.
Including all study phases the top three cost drivers of clinical trial expenditures are clinical procedure costs (15%–22% of total), administrative staff costs (11%–29% of total), and site monitoring costs (9%–14% of total).
A phase III failure is significantly more costly than a preclinical failure because each phase is associated with a certain amount of required investment.

It is significant that drug research is conducted ethically and efficiently. However, several issues can interrupt the successful delivery of trials. These include obstacles to patient

[30] https://www.sustainalytics.com/esg-blog/pharma-biotech-consolidation-2018/
[31] (Guido RV1, 2011)

participation, barriers to clinician participation, poor design, poor conduct, inadequate analysis, insufficient reporting and other difficulties such as complex consent procedures.

One of the most commonly reported problems with the conduct of multicenter randomized controlled trials (RCTs), however, is that recruitment is slower or more difficult than expected, with many trials failing to reach their planned sample size within the time window and funding originally expected.

The inadequate patient enrolled number represents the most common **cause of failure**. Up to 50% of clinical trials are delayed due to recruitment issues. Approximately 30% of enrolled patients will drop out over the course of a clinical study, and for many trials, recruiting enough new participants to continue is a serious challenge. Often sponsors apply for recruitment extensions to achieve the desired sample size resulting to the increasing cost of running trials and delaying the results from these ongoing trials. [32]

Due to poor recruitment and delays the financial losses can reach the amount of $8 million per day. [33]

If the required sample size is not achieved, the trial has less **statistical power.**

Extending the recruitment period and reaching the target sample size, the trials become more expensive and take longer, delaying the use of the results in clinical practice.

Also, the extended recruitment period can lead in trap because if trials last longer and costs much more than common then fewer trials will be conducted in the future and therefore less information will be available to patients. [34] (Associations, 2017)

3.4 Lack of awareness

Patients' awareness and perceptions of clinical trials, as well as attitudes of physicians, are some of the most important factors underlying low recruitment rates of patients into clinical trials.

[32] (McDonald AM1, 2011)

[33] https://www.mdconnectinc.com/medical-marketing-insights/digital-marketing-lowers-clinical-trial-recruitment-costs

[34] (Kaitin, 2008)

Lack of trust and awareness are often the main obstacles to research participation.
Multiple reasons have been identified as factors associated with research participant awareness.

One study, based on a survey of 2,000 physicians and nurses, has shown that nearly all physicians (91%), and most nurses (72%) feel comfortable discussing the opportunity to participate in a clinical trial with patients. However, physicians refer less than 0.2% of their patients into clinical trials, and nurses refer even fewer. [35]

Moreover, some of patients may have a general cognizance of clinical trials procedures, but they cannot imagine themselves participating on relevant studies.
Numerous studies have shown that most people aren't familiar with clinical trials opportunities and their possibilities.
For instance, one study of cancer patients showed that an astonishing 85% of respondents were unaware that participating in a clinical trial was an option for them. [36] (Farmer D, 2007)
A study from the Memorial Sloan Kettering Cancer Center stated that only one in four Americans have a positive impression about clinical trials and that over half of their surveyed physicians considered clinical trials only late in treatment. [37]

Figure 7 [38] Everyone plays a role in Clinical Research

[35] (S. Kogan, 2001)
[36] (Farmer D, 2007)
[37] (Liu, 2017)
[38] https://www.willseye.org/research/clinical-trials/clinical-trial-stick-people/

4. Marketing

4.1 The role of Pharmaceutical Marketing

Society sees pharmaceutical drugs as having "double personalities": as a conventional product that addresses certain consumer needs, and as something to which human beings have a fundamental right. As a conventional product, all rules of commerce should apply to it. However, many standard marketing practices must be modified owing to the sensitivity and complexity of these products.

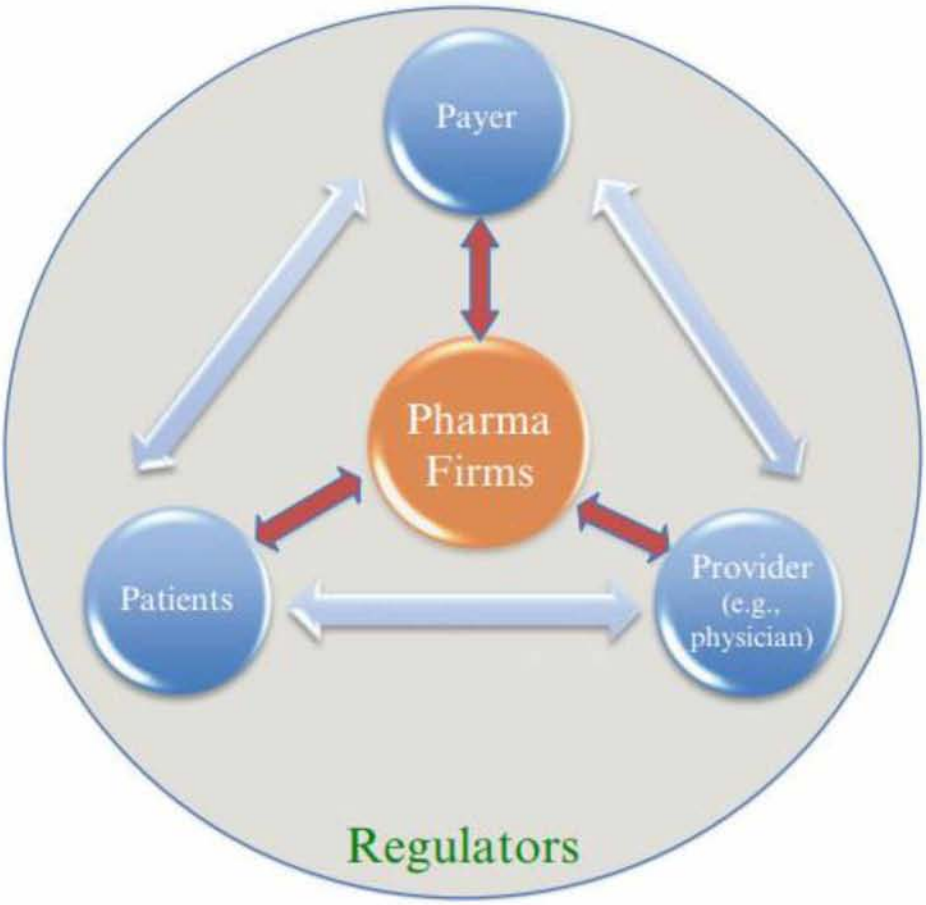

Figure 8 Players in Pharmaceutical Environment *(M.Ding, 2014)*

Successful marketing increases incentives to invest in research and development (R&D), and shapes that investment to make it more consistent with consumer preferences.
The main purpose of marketing is the exchange, in which two or more parties give something of value to each other to satisfy felt needs. Especially in pharmaceutical marketing the result of the feedback process from marketing to R&D is to increase consumer welfare. By advertising and promotion companies can accelerate the adoption of products designed to satisfy their target groups desires effecting an increasing expected returns from future R&D. (M.Ding, 2014)

The pharmaceuticals' target is mainly directed to toward physicians because influencing the physician is a key to pharmaceutical sales.
The overall mission of relationship marketing is to improve marketing productivity and enhance respective value for the parties involved in the relationship.

One of the most used and effective Marketing tools is **Marketing Public Relations (MPR),** which is used to complement and extend the reach of advertising in reaching markets where it may be expensive to advertise.
It refers to public relations activities designed to raise awareness, inform and educate target audiences and give consumers a reason to buy.[39]

Another useful marketing technique is the content marketing which focuses in creating, publishing and sharing information to the audience. The idea of sharing useful and informative content as a means of persuading decision-making has leaded to no longer expensive advertisements, assisting to attract greater consumer attention and creating profits to the company. [40]

4.2 Digital Marketing in the Pharmaceutical Industry

There is no doubt that traditional marketing has changed. There are countless channels for communicating value such as "offline" media, print (e.g. newspapers, magazine ads, billboards flyers), broadcast (radio, television ads) and other formats like mailings, telemarketing etc.
The rapid advance of digital media is changing the way people interact with and consume information.

[39] (Papasolomou, 2012)
[40] (Saxena, 2010)

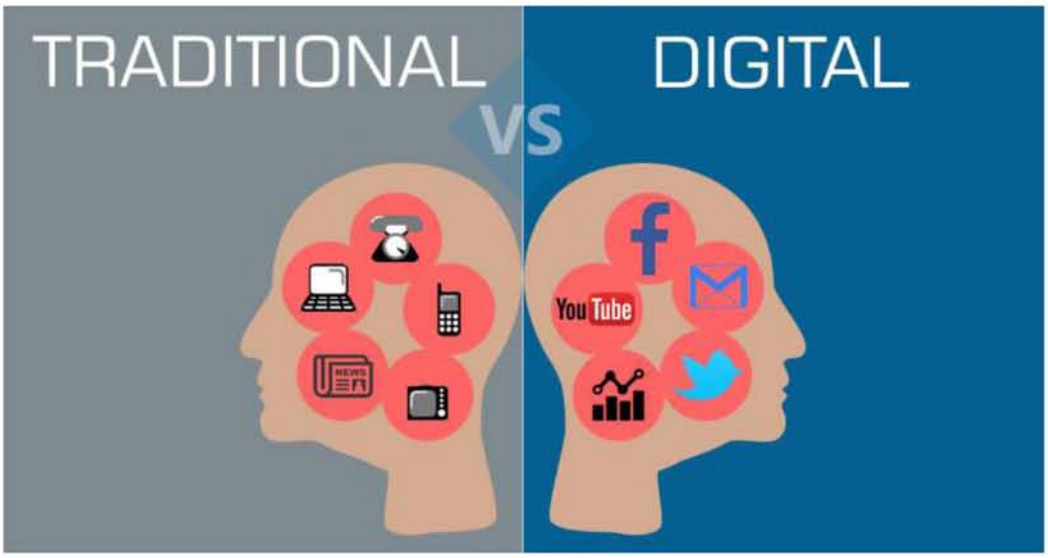

Figure 9 [41] Traditional and Digital Marketing

The organizational long-term success of promotional campaigns and the integration of marketing communications are affected by the effective use of the Internet. Today, advances in technology such as the Internet implementation in the marketing process is inexpensive, delivers instant international reach, offers great real time feedback, and reaches millions of people for whom the web is the center of virtually all communications. [42]

For an industry as profitable and large as pharmaceuticals, even the limited interest in the Internet has been more than enough to fuel the growth of a burgeoning e-health industry, as technology providers, service companies, consultancies and a host of start-ups seek their slice of a multi-billion-dollar research, development, sales and marketing pie. While the diffusion of Internet innovation into the pharmaceutical industry may have been unpredictable, literally thousands of conferences, publications, reports, magazines and even some practical research have accompanied it.

Digital marketing programs are already filling the gaps that traditional advertising methods cannot by reaching out to patients directly because the Internet, as a communications channel with individuals allows pharmaceutical companies to interact with purchasing decision-makers more consistently and on a virtual face-to-face basis. A wealth of opportunities exists for Internet health, wellness and disease management programme to build supportable, trust-based relationships.[43] [44]

[41] https://landerapp.com/
[42] (Anjali Gupta, 2015)
[43] (Piper, 2003)

Figure 10 Online Marketing Strategies[45]

Digital and social media have strongly influenced many businesses: publishing, entertainment, and retailing stores. They are also starting to have an increasingly dramatic effect on the pharmaceutical industry.

Pharmaceuticals are used to communicating directly with the patient under strict regulatory conditions (in the USA, New Zealand, and Canada) or to being prohibited from doing so (in the rest of the world). Today's global social media challenge this regulatory environment.

Some early efforts by firms to get engaged in social media (e.g., Sanofi 's VOICES program) have shown this engagement not to be trivial for pharmaceutical firms. It is essential that pharma companies are present on social media providing full and accurate information to the consumers. (Piper, 2003)

Online and in social media, patients speak freely about their experiences with pharmaceutical treatments. Patients are using social media as a major source of information and healthcare research. They can connect socially and share personal information. In some case, social media is often characterized as pages where participants can produce, publish, "filter", critique, rank, and interact with online content.

[44] http://www.fomatmedical.com/2017/07/marketing-strategies-clinical-trials/
[45] https://www.internetbusinessschool.com

Patients are rapidly dealing with their own health situation and using search engines to learn more about their symptoms and the various options for treatment.

Google and Facebook advertising are the most popular platforms, but pharmaceutical marketing departments should carefully evaluate their options to determine the media mix for them, since health issues and patients related information are truly sensitive.

With 1.92 billion users, Facebook is one of the largest "patient databases" on earth (second only to Google). Most patients and their caregivers of any age, gender, or ethnicity use the platform, making it an ideal platform for patient recruitment. Facebook offers advertisers a multitude of targeting options, including location, age, sex, demonstrated ethnicity, and the pages and groups a user engages with. With the proper approach, sponsors can reach a wider range of highly qualified prospective participants, thereby generating better leads for investigator sites at lower cost.
The right digital marketing program can decrease the likelihood of trial failure, save the industry billions, and help ensure patients have access to the live-saving new treatments they need. [46] (Papasolomou, 2012)

4.3 E-health Technology

Internet has changed and will continue to change the way the world communicates.
The number of people turning to the Internet to search for a diverse range of health-related subjects continues to grow.
This digital growth has led to the development of new concepts in health, including "e-Health", referring to health services and information delivered or enhanced through the Internet, related technologies and commerce.
E-health has the potential to greatly improve health service efficiency, expand or scale up treatment delivery to thousands of patients, improve patient outcomes and open commerce opportunities.[47]
Information systems, such as electronic health records (EHRs), mobile phones and computers can be of enormous value in providing health care in multiple settings. Health-related technologies are undergoing an evolution driven by the rapid emergence and dominance of the Internet in everyday life.

[46] (STEMPEL, 2018)
[47] (BSc, MD, MD, & Alejandro Jadad, 2005)

These developments have highlighted the benefits of these technologies with an emphasis on their potential to improve health education, disease surveillance, communication between patients and healthcare professionals, and support of clinical decision-making. [48]

The use of Internet and other new digital communication tools challenges the traditional communication model of pharmaceutical companies.
Reducing healthcare costs as well as offering quality healthcare treatment is becoming a priority for pharmaceuticals. The Digital era appears to be a powerful force of change and innovation for the healthcare industry worldwide. Pharmaceutical firms seem to respond to this development with basic E-strategies having similar tools and functionalities. [49]

Figure 11 E-Health Technology[50]

The "Taking the Pulse® Europe" survey of physician's Internet behavior (*Manhattan Research 2008*) showed that the Internet is becoming an increasingly relevant channel to multiply physician touch points. According to the major European countries, 95 % of physicians indicated that they use the Internet for professional purposes, 91 % agreed that the Internet improves the clinical capabilities and 84 % stated that the Internet is important to their professional practice.

The Internet can offer consumers the opportunity to search for information that is most relevant to their needs. In 2002, 80% of all adults online in the United States were estimated to have looked for health information.
With regards to Europe, a recent European Union (EU) survey on online health information showed that on average, nearly a quarter of Europeans (23%) use the Internet to obtain health information (this varies between countries, for example, 40% in Denmark and the

[48] (Liang, 2013)
[49] (Nilmini Wickramasinghe, 2004)
[50] https://wheelchronicle.com

Netherlands and 15% or less in **Greece**, Spain and Portugal) and approximately 40% of European find that it is a good way of obtaining health information. [51]

Undoubtedly Internet has a dominant place in our everyday activities and its usage met a considerable growth over the years. The internet users have surged and have reached the 57% of total population about 4.3 billion people. The penetration rate of internet is very high in Northern America and Europe as it reaches 90% of the population. Regarding the rest of the world (South and Central America, Africa, Asia and Oceania) the penetration rate reaches 65% of the population showing that it has chances for further penetration at these regions. Internet users spend 6.5 hours per day on average on the web. According to recent researches internet users allocate their time in social platforms, e-commerce sites, on line video platforms, newsy sites and searching platforms. [52]

Figure 12 Annual Digital Growth (KEMP, 2019)

Patients who have a deeper understanding of their diagnosis, prognosis and treatment deal better with their illness, are better consumers of health care and engage in healthier attitude to their daily life. [53]

Nonetheless, internet and digital information contribute to a change in the role of patients from passive to more active consumers, become more involved in their own healthcare, resulting in a more patient-center interaction between them and their doctors.[54]

[51] (McMullan, 2006)
[52] (KEMP, 2019)
[53] (Gustafson DH1, 1996)
[54] (MiriamMcMullan, 2006)

A study about THE INTERNET AND HIV / AIDS

A study regarding the use of the Internet as a source of information for people living with HIV/Aids showed that people who had access to online knowledge, earned substantial benefits in contrast with those who hadn't.
Especially, this survey of 174 HIV-positive men and 84 women found that those who accessed the internet regularly were less likely to have a detectable viral load, were more compliant with their medication, had a greater knowledge about their situation and demonstrated a greater knowledge of treatment options. [55]

Access to and effective use of health information can motivate individuals with chronic illnesses to actively participate in their health care, improving their mental and physical behavior.[56] (Kalichman SC1, 2002)

4.4 Strategies to increase recruitment

Research studies are essential to improving healthcare. However, many fail to recruit their planned number of participants. It is known that studies with few patients might miss clinically important effects. [57]
A variety of strategies has been reported; the most commonly reported strategy to improve recruitment are newsletters and mailshots, both to participants and to clinical staff to accelerate the trial. [58]

Posters and information leaflets about the research procedures have been also displayed in appropriate clinics and wards targeting the awareness of interested parties.
It is also proven that good collaboration and excellent communications across the involved individuals is extremely crucial in clinical trials.
Another commonly reported strategy is the investigators and international meetings. On these meetings the major processes and the trial Protocol are presented and discussed to the appropriate clinical groups and investigators, giving the opportunity to raise any potential concern and objection prior to the study initiation. Amendment of Protocol in the

[55] (Dahl, Peer support via the internet:What kind of online support is sought by individuals with chronic medical conditions?, 2006)
[56] (Kalichman SC1, 2002)
[57] (Mapstone J, 2007)
[58] http://researchonline

inclusion/exclusion criteria in an effort to improve recruitment has also performed in the past following someone's intervention during the investigator meeting. Focus group also, can provide insight into any issues, discussing the study progress, providing constant surveillance of views and targeting the participants' commitment. [59]

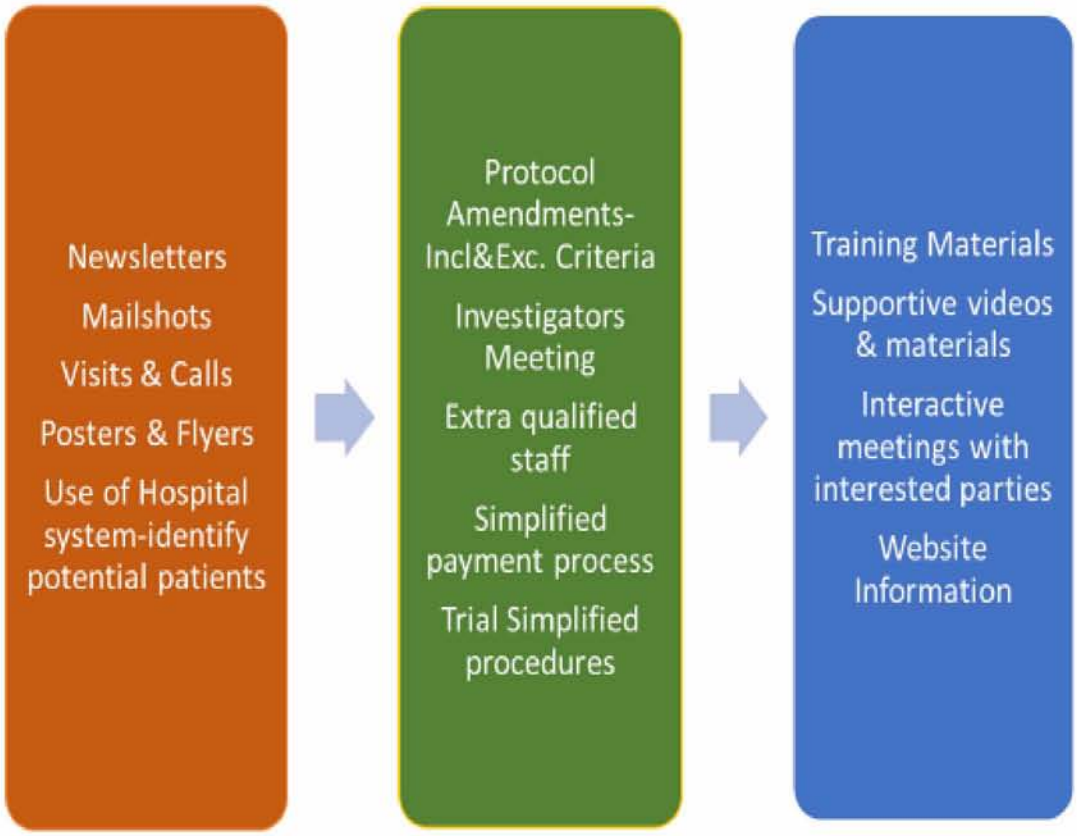

Figure 13 Reported strategies aiming to improve recruitment

Awareness and published studies

A valuable amount of studies has shown that public awareness can contribute in successfully completion of clinical trials.

A giant example of the importance of information is the media campaign was launched in 2008 where the awareness of randomized clinical trials was promoting.

[59] (Thomas W. LeBlanc, 2013)

Promoting public awareness of randomized clinical trials using the media: ***the 'Get Randomised'*** campaign. The '**Get Randomized'** campaign was a Scotland-wide initiative led by the University of Dundee in collaboration with other Scottish universities.

Television, radio and newspaper advertising showed leading researchers and patients informing the public about the importance of randomized clinical trials (RCTs). 'Get Randomized' was the central message and interested individuals were directed to the http://www.getrandomised.org website for more information. The main and most important result was that 49% of participants felt that the main message was that people should take part more in medical research. [60]

Figure 14 Get Randomised Logo (Mackenzie IS1, 2010)

Moreover, an Australian study presented the impact of a mass media campaign on participation rates in a National Bowel Cancer Screening Program.

An 8-week television-led mass media campaign was launched in selected regions of Australia in mid-2014 to promote Australia's National Bowel Cancer Screening Program (NBCSP) that posts out immunochemical fecal occult blood test (iFOBT) kits to the homes of age-eligible people. The campaign used paid 30-second television advertising in the entire state of Queensland but not at all in Western Australia. Other supportive campaign elements had national exposure, including print, 4-minute television advertorials, digital and online advertising.

The outcomes of this analyses showed that the higher intensity 8-week television-led campaign in Queensland increased the rate of kits returned for analysis in Queensland in comparison of the Western Australia. [61]

[60] (Mackenzie IS1, 2010)
[61] (Sarah J Durkin, 2019)

4.5 Online Marketing Strategies for Clinical Trial Recruitment

Attracting and enrolling eligible participants is the key to conducting successful clinical trials because this increases the opportunity for statistically significant results. The initial patients' target must be large enough to allow for possible rejection and drop-outs, while still assuring ample participants for the trial. [62]

Owing to the advancement of ever-sophisticated communication opportunities, today's marketing techniques can help clinical trial recruiters achieve their goals.
Apart from offline marketing strategies the use of online media is becoming more and more attractive because they are proving to be more cost-effective, interactive and tractable in comparison to offline media. The right digital marketing program can decrease the likelihood of trial failure, save the industry billions, and help ensure patients have access to the live-saving new treatments they need. [63]
A marketing and communication plan to physicians and patients is crucial to motivate them to participate and enroll, answering potential concerns and encouraging them to stay passionate until the study completion. (CATLEY, 2014)

Results from an Exploratory study showed that targeted recruitment using the social networking site Facebook has strong potential for yielding demographically representative samples of a specific group than landline telephones. Moreover, it is important to mention that this strategy was cost effective in comparison with many traditional methods.[64]

Nowadays, it is a common phenomenon that people of any age, gender or ethnicity are more involved in the decision-making process regarding their care choices.
With 1.92 billion users, Facebook is one of the largest "patient databases", offering advertisers multiple target options such as location, sex, ethnicity, age as well as relevant pages and connections users engaged with. (STEMPEL, 2018)

Studies have shown that Google, with over 660 million daily visitors is also one of the world's most popular websites in general, used for information gathering, shopping, email, navigation, cloud file storage, social networking, translation, and more.[65]
All the above, resulted in making Facebook, Google, and other websites an ideal platform for patient awareness and recruitment.

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[62] (CATLEY, 2014)
[63] (STEMPEL, How Patient Centricity and Digital Technologies Are Improving Clinical Trial Outcomes, 2018)
[64] (PhD, et al., 2012)
[65] (Margaret S Gross, Nancy H Liu, Omar Contreras, Ricardo F Muñoz, & Yan Leykin1, 2013)

With the proper approach and with a strong online presence sponsors can reach a wider range of highly qualified prospective participants, thereby generating better leads for investigator sites at lower cost. Using paid advertising and including targeted keywords in advertisements, websites, blogs and social media communications will increase the likelihood of the target demographic learning about a potential study. Once this attention is garnered, the potential subject can be directed to a website where all information and reasons to participate are available. (CATLEY, 2014)

Having achieved the awareness and recruitment target, then it is important to continue the communications process, so participants remain motivated to continue to the end of the study. (STEMPEL, 2018)

4.6 Google Ads

Google Adwords is the world's largest advertising network and it's consisted of network view (display) and network search (Search).

The above mentioned can provide sponsors {pharmaceutical companies or clinical research organizations (CROs)} the opportunity to target patients or caregivers who are actively researching treatment options for specific conditions or willing to be constantly informed about health news.
Nowadays, ads by Google are the most widespread and popular business model. It can be regarded as the breakthrough of advertising. [66]

It is an online advertising tool that offers businesses the chance to connect with their customers. Online advertising is all about getting the right message in front of the right person, at the right moment using keywords, location, demographics, and more to target their campaigns.[67]
With Google Ads, anyone can specify keywords based on what people are looking for.
These keywords will trigger the ad to be shown under the heading ''Sponsored Links'' amongst the rest google search results. Following that, clicked on specific ad, the user is directed to the website-page.

[66] (Petteri Kangas, 2007)
[67] https://support.google.com/google-ads/answer/7539883?hl=en

The Google Ads auction is the process that happens with each Google search. Once a question-search is made on Google, the search engine processes the request and runs the auction which will then determine the ad positions and each advertiser's cost per click (CPC), which is the amount an advertiser pays each time someone clicks on their AdWords ad. [68]

The CPC is determined by the competitiveness of chosen keywords, the maximum bids, and the Quality Scores.

Ad Rank determines the ad position where ads appear on the page or whether the ad will show at all.

Figure 15 Ad Rank Explanation (https://www.wordstream.com)

The campaigners define the price that they are prepared to pay for each click, and Google subsequently exploits its revenue by trying to calculate the formula (number of actual clicks) x (price paid for each click) (Petteri Kangas, 2007)

Monitor and manage

Using the google ads, there are tools to track and manage the performance and the cost of ad campaigns. These costs are incurred whenever a displayed ad is clicked. Displaying the ad (an impression) does not cost, however, the position of the ad (and therefore its visibility for users) is determined by the maximum amount of money an advertiser is willing to pay for the ad to be clicked, in an auction bidding system.

Higher ad ranking results in stronger exposure, due to the system ensures a display of ads that are truly relevant, a benefit to both users who seek information and advertisers who

[68] https://www.wordstream.com

want to show ads that are most likely to lead to clicks. (https://www.wordstream.com)

All the above-mentioned factors that can impact quality, like ad relevancy, the landing page experience, and that expected clickthrough rate, are all inputs affecting quality.

Moreover, supplementary technique with google ads is remarketing, which consists of static images, video and text ads that are placed on the Google Display and Google Search Network. In this way every site visitor can be ''marked'' with a special tracking code (cookies), and the advertiser can easily approach him/her anytime. Adjusting the remarketing on all landing pages of the desired campaign and especially on the initial page, the visitors can be recorded on a separate list where then the campaigner can use properly.
The main advantage with remarketing is that anyone can find those people who have shown enough interest to visit your website. These visitors are more likely to perform any activity compared to people who have not yet been to your website. [69]

5. Regulatory Permissions and Limitations

5.1 The Regulatory Framework in Greece

In effort of public health protection and pharmaceutical expenditure control, policies have been implemented by the Ministry of health which is responsible for creating, establishing and monitoring the legal framework in the pharmaceutical field.
The ministry of Health has designated the National Organization for Medicine (EOF) to be responsible for the marketing authorization products, supervising and approving clinical studies as well as providing post-authorization controls. [70]

EOF is also responsible for ensuring compliance with the existing legislation to the pharmaceutical advertising and can act urgently if any of discrepancies and non-compliance issues strike. [71]

[69] https://www.ppchero.com/ultimate-guide-to-google-ads-remarketing/
[70] (Companies, 2008)
[71] (Greece Pharmaceutical Advertising 2019, 2019)

5.2 Advertising and Regulations

Advertising of medicinal products means any form of door-to-door information, customer engagement or incentives designed to promote the prescription, procurement, sale or consumption of medicinal products.
In accordance to the legislation (44787/12-5-2017), the marketing authorization holder (pharmaceutical company is required to notify EOF regarding any advertising campaign of its business. [72]

Publicly advertising for pharmaceutical products which can only be obtained on prescription is prohibited. The ban does not apply to information campaigns approved by the competent authorities. (article 20.1) [73]
In general, the only advertising of medicinal products that can target the consumers is the one that isn't required doctor's prescription. (https://www.eof.gr/)

The EU General Data Protection Regulation (GDPR) has been applied across all EU Member states from 25 May 2018, is undoubtedly one more legal restriction that pharmaceuticals should deal with.
GDPR affect anyone or any company which may collects and processes personal data directly or indirectly, including IP addresses, location data etc. [74]

5.3 Internet-Digital applications

There are several types of Internet- Digital applications used in Pharmaceutical Marketing ''world''. The most known are the websites, Links, eDetailing, Enewsletter and social media.

[72] https://www.eof.gr/

[73] SFEE Code 2017
[74] (Tankard, 2016)

Figure 16 Digital applications[75]

In accordance with the article 27.3 any of the pharmaceutical companies can have a main corporate website, including company's profile, history and news. It may also provide public awareness, texts on health prevention issues but they aren't allowed to link them with any pharmaceutical product of the company.

Texts and artworks - and any major revisions - should be submitted to the EOF in accordance with and comply with Circular 43631 / 14-6-2012.

Moreover, the content and information should be presented in a neutral and objective manner with clear reference sources. The phrase should be appeared: "This information is intended for general information and information to the public and under no circumstances can they replace the advice of a doctor or other competent health professional".

The e-Detailing is defined as the provision of electronic promotion forms, eDetails to healthcare professionals in promotion and information such as Video, webcasts etc. (article 27.4.2.). Pharmaceutical companies must regulate the frequency of distribution of e-Details in a way that meets the needs of meaningful information.

Figure 17 e-Detailing [75]

[75] https://www.bluenovius.com/healthcare-marketing/point-of-care-advertising-pharma/

Following the article 27.6, the use of social media is growing, and both public and health professionals use these channels as a means of informing about health-related issues. However, the use of social media should be carefully considered regarding ensuring the quality and validity of the information it transmits and its objectives. (SFEE Code 2017)

5.4 Regulations about clinical trials and marketing

The advertising of clinical trials in Greece is strictly regulated and complex. On September 2018 National Ethics Committee (NEC) has published guidelines about the acceptable advertising. In accordance with this article, it refers that non-interactive information (such as printed or electronic leaflets, audio messages, posters, media listings) is permitted but registration on social media is not allowed.

Especially isn't allowed the Interactive information (web-based platforms with **personal data entry** of the candidate participant) and the collection by a company of sensitive personal information by electronic or telephone questionnaire.
It is necessary that the company should submit for NEC consultation any text/proposal, the content of the update as well as the ways and means of information material distribution. https://www.eof.gr/)

Figure 18 Regulations[76]

[76] https://www.businessnewsdaily.com

6. Campaign-Easy Friendly WebPage development

6.1 Building awareness- The Be Part of the Future *Campaign*

Planning ahead can assist pharmaceutical companies to anticipate challenges and ensure the successful conduction of clinical trials with limited capital losses and time.

The ***Be Part of the Future*** Campaign proposed in this thesis, aims to raise public awareness about the importance of clinical studies, encourage greater participation and willingness by patient populations, while offering the opportunity to researchers to develop potential innovative therapies.
The campaign goal: The main point the pharma company wants to get across is to increase people awareness about the clinical research and trial phases, by making them familiar with the clinical trials benefits as well as with the participation procedures.

The resources: It is necessary to determine the budget and the time needed for the awareness campaign. Budgets are always an estimation of costs, based on experience and guesswork assumptions. Therefore, it is likely that the budgets may have been either under or over estimated. On ***Be Part of the Future*** campaign the amount will be defined and invested by two different company's departments, R&D and Marketing-Communications. The two departments will provide an amount of their annual budget for the campaign initiation.
The awareness campaign will take place during September and October; 6 months later, any received feedback will be assessed and continuing the ongoing educational purpose.

Target the General Population: Firstly, the defined target group is consisted of people who know very little about research. This should especially include people who have relatives impacted by a disease, as they can act as trusted referral sources to push relatives to seek out research participation. At a later stage, the target will be extended to people who are actively involved in the medical field, and patients who regularly take part in clinical trials, in order to re-engage them.
On this campaign, people with no Internet knowledge-skills will be excluded from the chosen audience, since the majority of activities and advertisements will be presented digitally.

Promoting Channels: Initially, the ***Be Part of the Future*** campaign will start with *transit advertising*, namely advertising placed in or on modes of public transportation like subway

and airport. With transit advertising, content and educational information about clinical research can be placed anywhere on public transportation, providing high visibility to the passengers daily. Apart from print advertisement-posters, digital advertising on plasma or LCD screens will also be used, offering the choice of barcode where people can scan it and lead them to the informational proposed website (user friendly webpage): www.BEpartofthefuture.com .

In parallel the campaign will run in Hospitals, in health centers and in Private clinics. By presenting information about clinical studies in places where clinical trials can be conducted or already run, the chances for awareness and effectiveness to attract potential participants are significantly increased.
Some of the posters are displayed below.

Figure 19 A proposed campaign poster

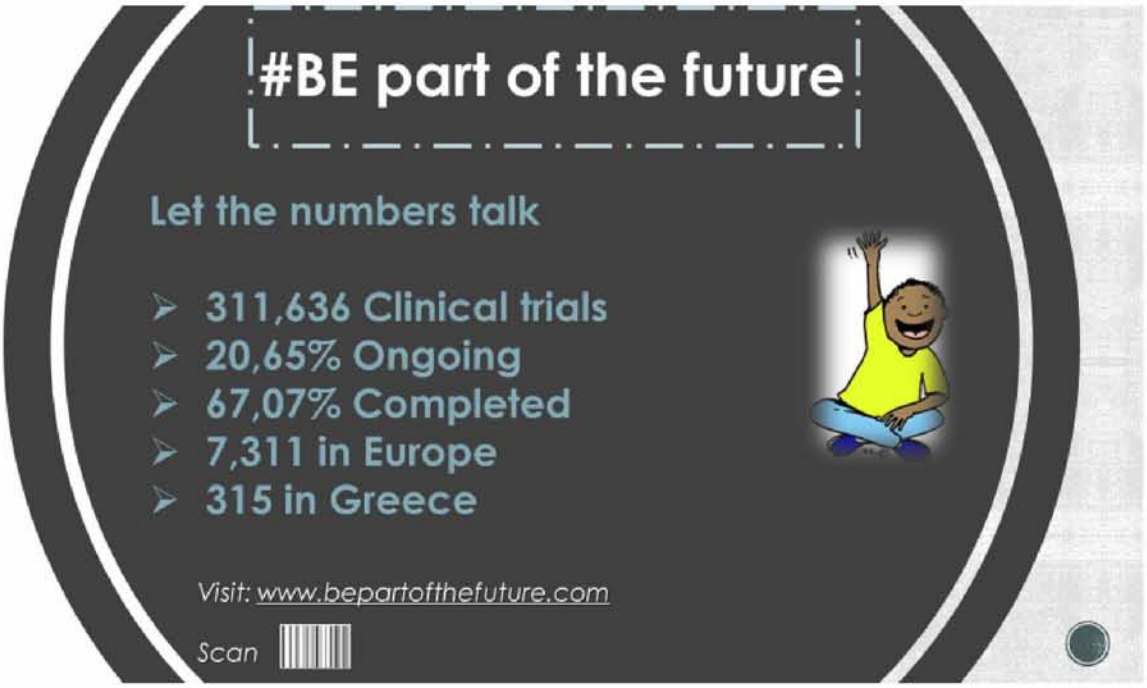


Figure 20 A proposed campaign poster

Apart from the educational posters and advertisements, several sponsored conferences will be organized so as to support the campaign.

Every year many National Congresses per disease category are held, covering a lot of different issues varying from medicine and innovation to health news. Usually these meetings are sponsored by Pharmaceutical companies, Organizations such as Hellenic Society of Cardiology and rarely from Ministry of Health. Considering all the above, the campaign can be enforced, participating actively on these meetings, presenting company's performance, educating the audience regarding the clinical trials as well as promoting them to visit the company's website for more information.

Undoubtedly, campaigns are moving towards social media era. However, on this campaign the use of social media might not be applicable at this moment due to numerous regulations ban regarding the exposure of extremely sensitive personal information.

6.2 Partnerships

Partners make any awareness campaign valuable and powerful, especially when the partner provides access to a larger audience.

During the campaign, it is essential to create strong partnerships with members of our community or other influencers who care about these sensitive issues which become even more impactful when they publish their own story and experience in a clinical study participation.

Top Researchers-Recruiters

Top recruiters play an important role in study execution including the development of a strategy to maximize enrollment and assure patient retention. Certainly, the well-educated and enthusiastic Principal Investigator plays a crucial role in high recruitment. During the campaign the investigators' contribution is undoubtedly vital. Their participation in clinical trials campaign will motivate and encourage the audience due to their position over the years and their scientific background, driving the public to show interest and trust in their words.

Influencer outreach boosts patient awareness

The term "influencer" refers to a diverse group of people within the patient recruitment space. An influencer can be a patient presenting a disease, a patient's caregiver, a celebrity with a condition or a community leader. Any individual that has an engaged audience, has an accessible channel (social media, blog, or website) to share information, and is passionate about spreading awareness for a cause, is a potential influencer.

For the above reasons, such influencers will support the awareness campaign, persuading their audience to visit the webpage for more information, creating doubts and thoughts about all their previous beliefs and prejudices.

6.3 Find the stakeholders and build strong relationships

Apart from campaigns with Investigators and influencers, building strong relationships with the government, with third parties such as pharmacies, advocacy groups and regulatory authorities is crucial.

Figure 21 Building Strong Relationships[77]

More and more pharmacists move from the traditional dispensing role to become more actively involved in patient care, providing them with medical information, education and pharmaceutical care services.

Due to their relationship quality, patient satisfaction, and their commitment, pharmacies can play an important role in a company's awareness campaign.

The collaboration with the pharmacies has two ways of advertising: posters and short videos playing on tv screens. The necessary equipment will be provided through the campaign sponsor. In that way the awareness of the audience regarding clinical trials will be boosted as pharmacies are considered hubs of potential participants, because they are visited

[77] https://www.liquidplanner.com

directly by patients and indirectly by caregivers who are the most important stakeholders for the clinical trials.

This project cannot be conducted without government support and cooperation.
Due to the fact that all marketing strategies should be followed by NEC and EOF regulations before each innovative step, it is imperative the webpage design as well any innovative ideas to be submitted first to Regulatory affiliate for approval. According to the Greek legislation, NEC should be aware of any pharmaceutical marketing strategies, commercial and advertisement, so the company during the campaign should be aligned with all obligatory laws, showing excellent performance and creating solid relationships.

Moreover, studies have shown that the involvement of families, researchers, emergency medicine physicians etc. has provided with unique perspectives that may help increase the recruitment of Randomized Clinical Trials up to 30 percent following proposals and ideas that these groups posed.[78]
The **#Be part of the future** campaign will rely mostly on interactions and synergies with patients' groups based on mutual respect and transparency. These support groups guided usually by patients offer a variety of services, including consultations, group therapy, team building activities, provide them with tips on how to cope and adapt their conditions into their lifestyle. These advocacy groups play a significant role in informing and supporting patients, as well as safeguarding their rights.

By building these partnerships, more and more patients will become familiar with clinical trials importance and procedures, which will as a result drive the patients' best understanding about their opportunities in new treatments through their participation in clinical research. Taking into consideration that many people in these groups have participated at least once in clinical trial, sharing their experiences, truths and concerns is certainly priceless for achieving the awareness goal.

[78] (Minneci PC, 2016)

6.4 Google Ads

The fact that the majority of the population uses search engines, in conjunction with the ability to target messages based on search key words, turn online advertising and specifically google ads to a powerful tool for this campaign. As a result, the next and important step of this project is the use of google ads. The main role of google ads is to lead potential patients to the new company's webpage. This can be achieved by presenting the right message to the right person, at the right time.

With the completion of aforementioned marketing techniques, the company will have already achieved one big part of the campaign's mission which is to make "noise", to create prominence and capture the public's attention. Moving forward, it is essential to further enhance the popularity of **#BEpartofthefuture** project. Having an online presence, the company's chance to reach more interested and informed participants is increased, resulting in more quick recruitment which is the main reason and purpose of this thesis.

Using the technology and google ads techniques, the **#BEpartofthefuture** will display at the top of bottom in the user main screen, every time someone enter keywords like pain, disease, hospital, new drugs etc. These keywords will have been predefined and linked to the webpage-target www.BEpartofthefuture.com.
Moreover, including demographic characteristic in the initial campaign set up, allows to reach a specific set of potential interested individuals who are likely to be within an age range, gender, parental status, or have medical history.

Figure 22 Google Ads Use[79]

[79] Google.com

6.5 Incorporate a new extra easy friendly page -link into the homepage

All the above techniques aim to direct people to the website which is the last and most important step of this campaign.
The main website is the backbone of company's business and entrepreneurship, supporting the company's philosophy and vision, while also providing accurate information and services to the consumers. In addition, the website is the communication link that any business needs.
The objective on this campaign is to incorporate a new extra easy customer friendly page into the main company-pharmaceutical main homepage. In that way the campaign starts being more specific, than earlier where the target was to raise public awareness.

Considering that websites are the customer's first impression, it is vital to design an attractive one-page, with useful content and simple navigation. The website should provide consumers quick loading times and the best surfing experience. The main goal is to ensure good and accurate content, allowing visitors to see the company's face in a virtual space, causing traffic with articles reposts and shares, expanding the knowledge and the clinical trials mission. By creating respected and didactic content in the digital page, trust and credibility are going to be built, helping patients and non-patients to feel safe and encouraged of what they read.

As more patients ''go online'' the use of Internet as a source of information and education has become more common and more popular across age groups.
It is very crucial that the new additional page into the main company's website is more educational and does not aim to direct communication. At a later stage, the aim will be to find new potential patients for ongoing or future studies.

Taking into consideration all the above the structure of this page will have specific features and design.

At the main company's website, on the top of the main menu the additional page called #BEpartofthefuture will be featured.

Figure 23 Simulation of the company's webpage incorporating the ***BEpartofthefuture*** *Tab.*

By clicking the **BEpartofthefuture tab**, a new page will open,showing the detailed new smart informative page.

This page is designed in such a way that it will support, inform, and help patients that are interested in participating to a clinical trial.

There will be four main categories in this page: Clinical Trials, Healthcare professionals, Patients & Caregivers and News. A Search option where someone can find all the ongoing studies is presented seperately from the main categories.

Figure 24 Stimulation of the new extra tab

More precisely, a series of questions are presented with smart and simple answers when opening the **Clinical Trials tab**. Moreover, the most important information is offered digitally via videos and motion images.

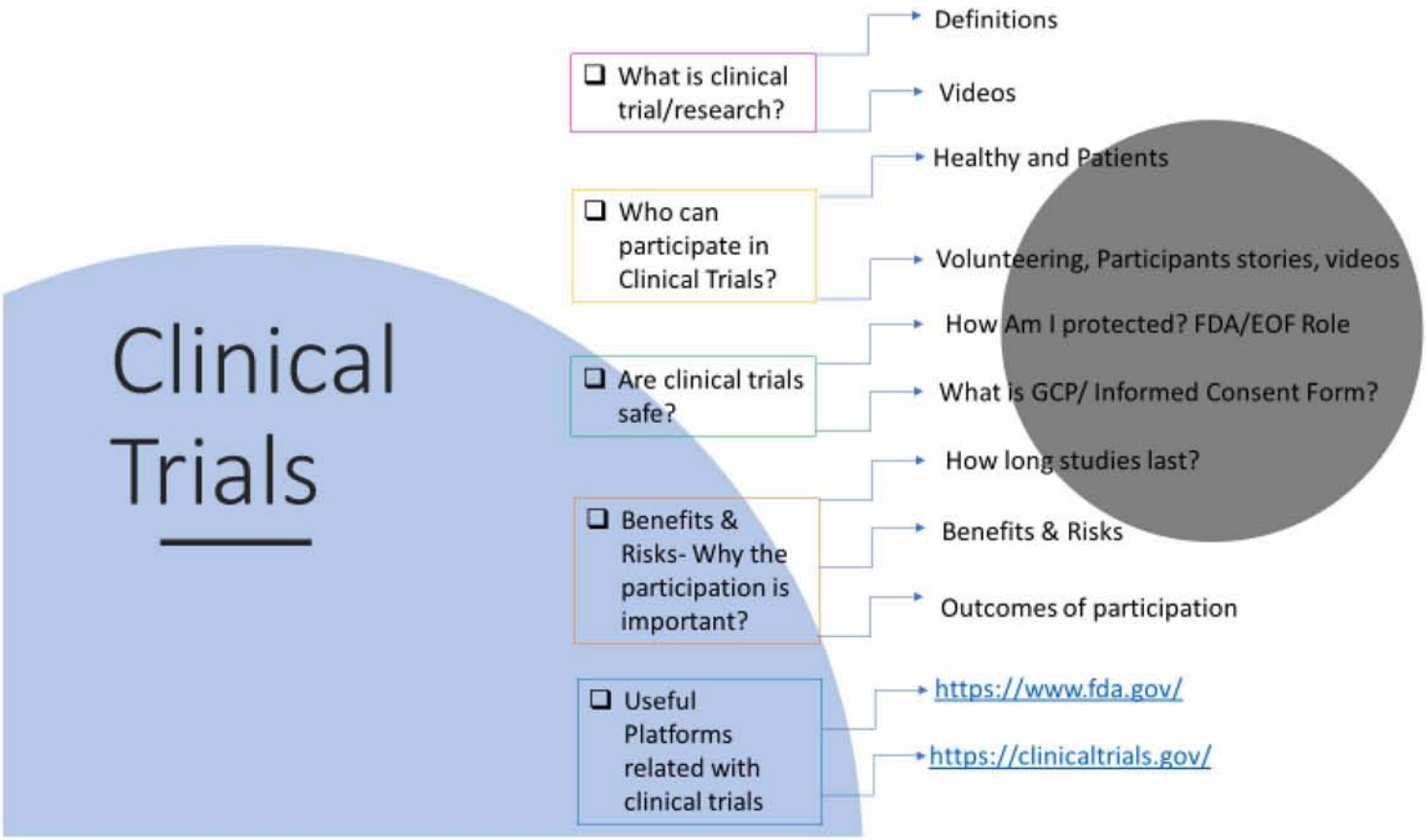


Figure 25 Stimulation of the Clinical Trials Tab

The next main tab in the landing page is the **Healthcare Professionals**. By connecting study participants to clinical investigators together, the recruitment process can be quicker, more accurate, and more personal than ever.

This tab will include a list of top clinical sites like a database based on geographically position, with contact details and linked relevant researchers that can be reached.

Moreover, an additional subpage will be populated when someone clicks on a specific hospital (mostly University Hospital) site, which will include all the ongoing clinical studies.

The **patient and caregivers tab** are of high importance as they can boost and influence patients' awareness and trust. Patient Advocacy Groups (such a "K.E.F.I. of Athens" Association of Cancer Patients of Athens) [80]are non-profit support organizations, which play a substantial role in patient socialization, representing patient's rights internationally.

The main purpose of this tab is to provide free and organized all the available groups with contact information and the URLs of their main homepages.

[80] https://www.anticancerath.gr/

The last tab is ''**News**'', where news about clinical trials all over the world will be daily posted and constantly updated. This portal will cover news related to the following Pharma Categories:

- Research & Development News
- Conferences & Events related to Clinical Trials
- Regulatory Affairs – Study Drugs Approvals
- Completed Studies Results

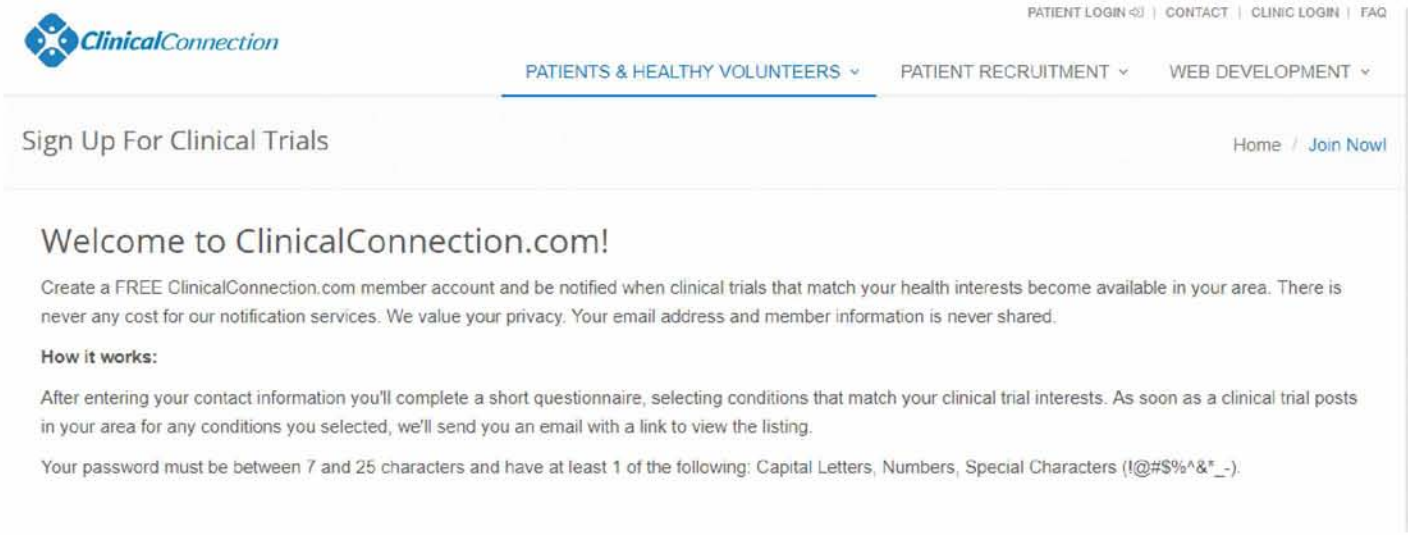
The main purpose of this section is to provide new and accurate information about clinical trials within an interesting and nice digital environment where everyone can surf easily, get well informed and become familiar with pharma world and clinical research. An important point to this section is to provide patients with prompt feedback on their participation results, including a general idea that shows in which way they have contributed to the development of a new, better and advanced treatment.

6.6 Relevant already used platforms

Over the last decade, several digital platforms have been designed by pharmaceutical companies and by authorities, attempting to improve the quality and the quantity of clinical studies. These webpages are mostly used and known in USA.

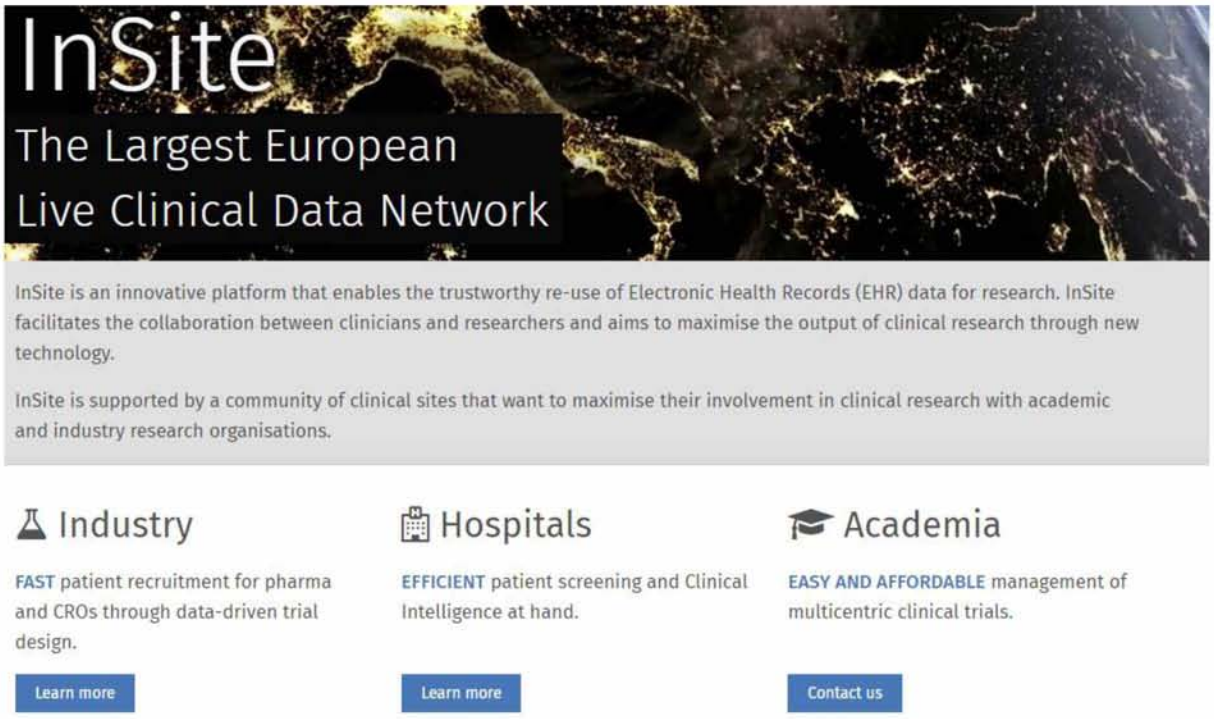
- Clinical Connection: Clinical Connection site is a database where people can register, create a profile and outline their medical history. The ultimate purpose of this site is that the system scans all recorded profiles and sends notifications to patients that could be potential participants every time a new clinical trial may start.

URL: https://www.clinicalconnection.com



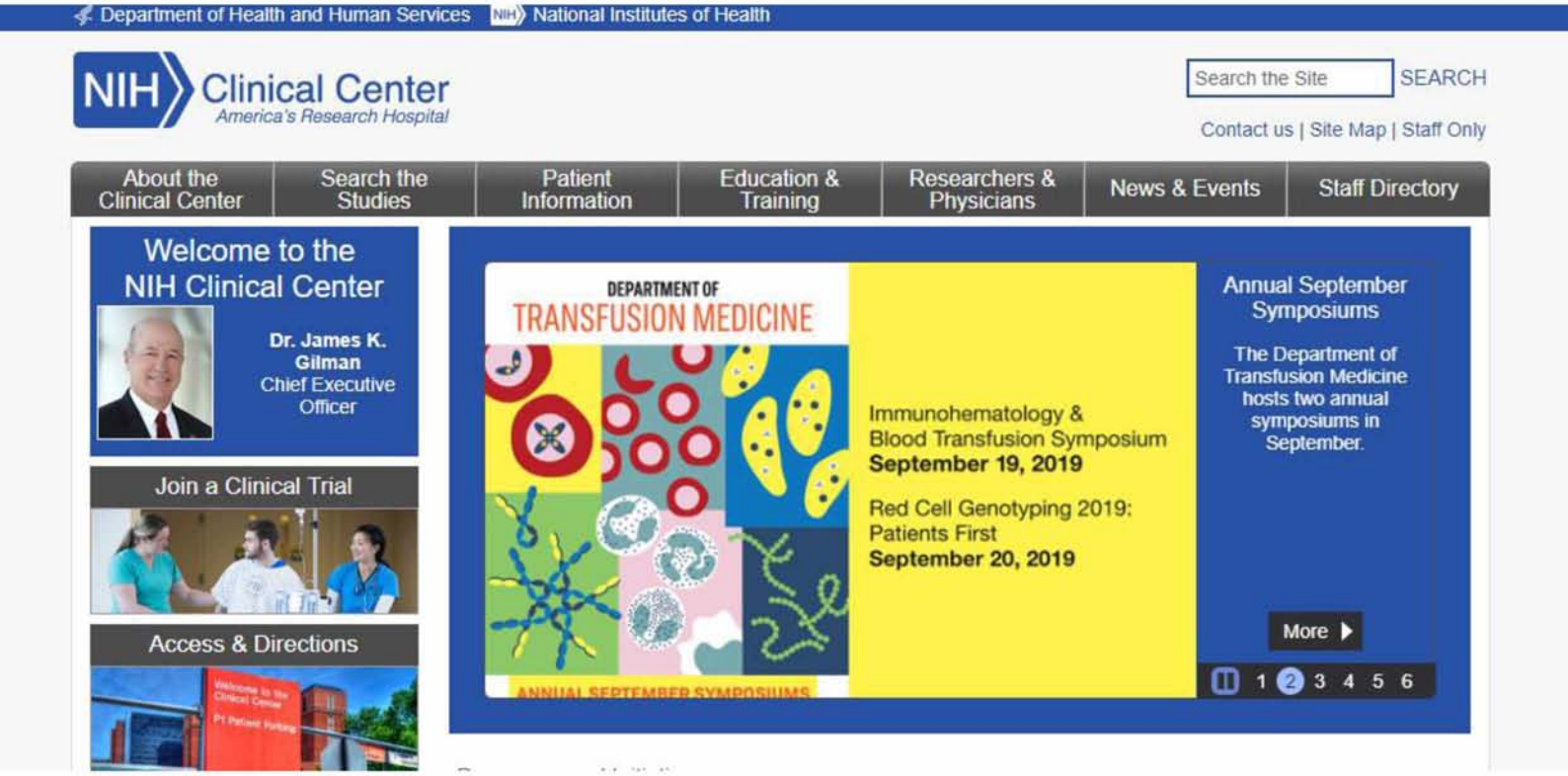
- Insite Platform: This European webpage is designed to connect physicians to researchers, through a secure network, by utilizing all clinical sources and combining data from different sites.

URL: https://www.insiteplatform.com/



- National Institute of Health: This page belongs to the America's Research Hospital, providing plenty of information, news and educational material about clinical trials.

URL: https://clinicalcenter.nih.gov/



6.7 Obstacles in Greece

The legal framework regarding the conduction of clinical trials in Greece is strict and complex, and it is even more challenging when it comes to their advertisement.
Due to the several regulations and bureaucracy, many campaigns and (digital) marketing strategies in clinical trials cannot get approved.
The Greek authorities, ministry of Health, EOF and NEC sometimes act conservatively as they have low flexibility in adjusting to current trends regarding clinical trials.

Another barrier in informing public about clinical trials is the biased perceptions. A significant number of patients, believe that by taking part in clinical studies, they face risks, and see

themselves as ‘’test animal’’ or ‘’guinea pigs’’. Especially, there is a misconception that all clinical studies and all phases involve a placebo and participants get no treatment which leads to worsening their condition.[81]

Due to the above perceptions, similar clinical trial campaigns may not attract patients as the latter cannot understand and appreciate the positive impact of their participation to such a trial.

Last but not least, the extended financial crisis has had a negative impact on Research and Development investments due to the lack of enough funds. Claw back and rebate have created significant financial pressures and instabilities within Greek health systems and firms, as the pharmaceutical companies should be complied with the requested measures, by returning to the government considerable amount of funds.[82]

The pharmaceutical companies could not be an exception, as they struggled to invest in Research on new drugs, let alone in clinical trials. These financial barriers could prevent pharmaceutical companies from investing in innovative marketing strategies and in future campaigns that could improve the clinical trials

7. Discussion-Conclusion

In the everchanging era of the pharmaceutical industry, mainly due to economic downturn, biotechnology and pharma companies are still on top of the Industries. One of the main reasons is that these companies have invested heavily in innovation and research.

Clinical research is the most valuable objective for pharmaceuticals success; as clinical research is being constantly evolving, companies should find new ways and methods to stand out and achieve a sustainable competitive advantage over the other companies.

One way to create competition and win is to accelerate the stages of a drug development, being proactive and optimizing the critical design thinking. By combining the science with marketing strategies in a digital perspective-view, a company can make a difference in pharmaceutical market.

[81] (Quinn, 2007)

[82] (Projecting pharmaceutical expenditure in EU5 to 2021: adjusting for the impact of discounts and rebate, 2018)

With a campaign like the **#BEpartofthefuture**, a company can create new knowledge bases, accelerate the designing of new medicines and medicinal choices, as well as improve the existing treatment choices.

Ideas and new strategies using the digital marketing, like the thesis study case can raise public awareness of clinical trials participation and fasten the completion of clinical trial and getting the approval for the market. However, further efforts and studies may be required to influence patients' decisions to contribute in clinical research. It is crucial that people get convinced on the clinical trials benefits, because with their own participation in clinical trials, they contribute to the drug development and approval process, resulting in expeditious access to advanced beneficial medicines.

Pharma urgently needs to establish best practices to overcome difficulties and obstacles that can delay any drug development procedures in future.
All potential complications that can occur delays to the identification of a new treatment, should be recognized and analyzed, designing a corrective and preventing plan, as it is hard for a company to stay stationary and rigid, let alone when these problems may have impact in the quality of patients' life

Bibliography

Greece Pharmaceutical Advertising 2019. (2019, June 17). *ICLG.com*.

A. Mahmud, M. O. (2018). Barriers to participation in clinical trials: a physician survey. *Current Oncology*.

Alexander Schuhmacher, O. G. (2016). Changing R&D models in research-based pharmaceutical companies. *Journal of Translational Medicine*, 14:105.

Americans' views on research and the Tuskegee Syphilis Study. (2001). In S. C. Vicki SFreimuth, *Social Science and Medicine* (pp. Volume 52, Issue 5, March 2001, Pages 797-808).

Anjali Gupta, K. J.-C. (2015). Clinical trial management of participant recruitment, enrollment, engagement, and retention in the SMART study using a Marketing and Information Technology (MARKIT) model. *Elsevier*, 185-195.

Asbjørn Hróbjartsson, M. a. (2001). Is the Placebo Powerless? — An Analysis of Clinical Trials Comparing Placebo with No Treatment. *the new england journal of medicine*, 344:1594-1602.

Associations, I. F. (2017). THE PHARMACEUTICAL INDUSTRY AND GLOBAL HEALTH. *Facts and Figures* .

Basil Achilladelis, N. A. (2000). The dynamics of technological innovation: the case of the. In *Research Policy* (pp. 535–588).

BSc, H. O., MD, C. R., MD, M. E., & Alejandro Jadad, M. D. (2005). What Is eHealth (3): A Systematic Review of Published Definitions. *Journal of Medical Internet Research*.

CATLEY, J. (2014, February 11). Online Marketing Strategies for Clinical Trial Recruitment. *MD CONNECT*.

Chang, S.-C. C. (2008). Adaptive design methods in clinical trials – a review. *Orphanet Journal of Rare Diseases 20083:11* .

Choosing the right animal model for infectious disease researchConsiderations for Infectious Disease Research Studies Using Animals. (2018). In J. Swearengen.

Companies, H. A. (2008). The Pharmaceutical Market in Greece Facts & Figures. Athens.

Dahl, S. (2006). Peer support via the internet:What kind of online support is sought by individuals with chronic medical conditions. *Journal of Medical Marketing*, Vol. 6, 4 268–275.

Dahl, S. (2006). Peer support via the internet:What kind of online support is sought by individuals with chronic medical conditions? *Journal of Medical Marketing*, 268 – 275.

DiMasi, J. A. (2003). The price of innovation: new estimates of drug development costs. *Journal of health economics* , 151-185.

Drager N, B. R. (2001). *Globalization: changing the public health landscape. Bulletin of the World Health Organization 2001;79:803.*

Evelyne Shuster, P. (1997). Fifty Years Later: The Significance of the Nuremberg Code. *N Engl J Med*, 337:1436-1440.

Farmer D, J. S. (2007). Attitudes of African American and low socioeconomic status white women toward medical research. Journal of Health Care for the Poor and Underserved. *PubMed*, 18:85–99.

Group, I. E. (1996). ICH HARMONISED TRIPARTITE GUIDELINE. In *GUIDELINE FOR GOOD CLINICAL PRACTICE.*

Guido RV1, O. G. (2011). Modern drug discovery technologies: opportunities and challenges in lead discovery. *PubMed*, 830-9.

Gupta, R. M. (2010). Adaptive design clinical trials: Methodology, challenges and prospect. *US National Library of Medicine* , 201–207.

Gupta, S. K. (2012). Use of Bayesian statistics in drug development: advantages and challenges. *International Journal of Applied and Basic Medical Research*, 2(1): 3–6.

Gustafson DH1, H. R. (1996). Impact of a patient-centered, computer-based health information/support system. *PubMed*, 1-9.

J.Deans, P. C. (2018). Clinical trials, Seminars in Pediatric Surgery. *Science Direct*, Volume 27, Issue 6, December 2018, Pages 332-337.

Kaitin, K. (2008). Obstacles and opportunities in new drug development. *Nature publicing group*, Volume 83 number 2.

Kalichman SC1, W. L. (2002). Closing the digital divide in HIV/AIDS care: development of a theory-based intervention to increase Internet access. *US National Library of Medicine National Institutes of Health*, 523-537.

KEMP, S. (2019, January 30). DIGITAL 2019: GLOBAL INTERNET USE ACCELERATES. *We Are Social*.

Liang, T. K. (2013). Pharmaceutical digital marketing and governance: illicit actors and challenges to global patient safety. *Globalization and Health*.

Liu, A. (2017, January 18). Low clinical trial recruitment rates have poor physician communication to blame: report. *Fierce Biotech*.

M, A. A. (2015). *International Journal of Management Science and Business Administration.*

M.Ding. (2014). *Innovation and Marketing in Pharmaceutical Industry.*

Mackenzie IS1, W. L. (2010). Promoting public awareness of randomised clinical trials using the media: the 'Get Randomised' campaign. *US National Library of Medicine National Institutes of Health*, 128-135.

Mapstone J, E. D. (2007, April 18). Strategies to improve recruitment to research studies. *Cochrane Database of Systematic Reviews*.

Margaret S Gross, B., Nancy H Liu, P., Omar Contreras, B., Ricardo F Muñoz, P., & Yan Leykin1, P. (2013). Using Google AdWords for International Multilingual Recruitment to Health Research Websites. *JMIR*.

McDonald AM1, T. S. (2011). Using a business model approach and marketing techniques for recruitment to clinical trials. *PubMed*, 12(1):74 .

McMullan, M. (2006). Patients using the Internet to obtain health information: How this affects the patient–health professional relationship. *ELSEVIER*, 24-28.

Minneci PC, N. K. (2016). Improving Surgical Research by Involving Stakeholders. *US National Library of Medicine National Institutes of Health*, 579-580.

MiriamMcMullan. (2006). Patients using the Internet to obtain health information: How this affects the patient–health professional relationship. *Elsevier*, 24-28.

Nilmini Wickramasinghe, A. F. (2004, December). A Framework For Assessing E-Health Preparedness. *Americas Conference on Information Systems*.

Papasolomou, I. (2012). Social Media: Marketing Public Relations New Best Friend. *Journal of Promotion Management*.

Petteri Kangas, S. T. (2007). Ads by Google and other social media business models. JULKAISIJA ñ UTGIVARE .

PhD, Y. F., Suzanne M Garland MBBS, M. F., Elya E Moore, P., Yasmin Jayasinghe MBBS, F., Ashley Fletcher, M., PhD, S. N., & Bharathy Gunasekaran John D Wark PhD, M. F. (2012). Web-Based Recruiting for Health Research Using a Social Networking Site: An Exploratory Study. *JMIR*.

Philip Sedgwick, s. l. (2011, September 28). Phases of clinical trials. *BMJ*, p. 343.

Piper, L. L. (2003). Digital strategies in research and development (R&D). In *Digital Strategies in the Pharmaceutical Industry* .

Prayle, A. P. (2012). Compliance with mandatory reporting of clinical trial results on ClinicalTrials. gov: cross sectional st. *Bmj*, 344 (2012): d7373.

Projecting pharmaceutical expenditure in EU5 to 2021: adjusting for the impact of discounts and rebate. (2018). In J. Espin, *Applied Health Economics and Health Policy* (pp. 803-817).

Quinn, G. P. (2007). The Guinea Pig Syndrome: Improving Clinical Trial Participation among Thoracic Patients. *ELSEVIER*, 191-196.

S. Kogan, Q. Z. (2001). Problems and challenges in patient information retrieval: a descriptive study. *NCBI*, 329–333.

Sarah J Durkin, K. B. (2019). Impact of a mass media campaign on participation rates in a National Bowel Cancer Screening Program: a field experiment. *BMJ*.

Saxena, S. (2010). NSB Management Review.

STEMPEL, D. (2018, Jaunuary 17). How Patient Centricity and Digital Technologies Are Improving Clinical Trial Outcomes. *MD Connect*.

STEMPEL, D. (2018, Jan 17). How Patient Centricity and Digital Technologies Are Improving Clinical Trial Outcomes. *MD Connect*.

Tankard, C. (2016). What the GDPR means for businesses. *ELSEVIER*, 5-8.

Thomas W. LeBlanc, M. M. (2013). Overcoming Recruitment Challenges in Palliative Care Clinical Trials. *US National Library of Medicine* , 277–282.

Utley, G. J. (1992). *The Nazi doctors and the Nuremberg Code: human rights in human experimentation: human rights in human experimentation. Oxford University Press, USA, 1992.*

[i] Novel therapies: Novel drugs are often innovative products that serve previously unmet medical needs or otherwise significantly help to advance patient care and public health. New molecular entities (NMEs) have chemical structures that have never been approved before. https://www.fda.gov