Universidade de Lisboa

Faculdade de Farmácia

THE SCIENTIFIC IMPACT OF COMMERCIAL AND NON-COMMERCIAL CLINICAL TRIALS IN PORTUGUESE INSTITUTIONS

Maria Pinheiro de Azevedo Andrade

Dissertation supervised by Dr. Catarina Madeira and co-supervised by Professor Dr. Helder Mota-Filipe.

Maser Degree in Biopharmaceutical Sciences

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ABSTRACT

Background: The pharmaceutical industry is the lead promoter of clinical studies across the world and its focus is on the company's molecules which are patented. Although there are fewer non-commercial clinical trials, the information provided in these studies is vastly important for the wellbeing of the society, not aiming at the protection of commercial interests. Concerning the impact of both types of clinical trials, commercial studies are frequently published in high-impact scientific journals, given the complexity and dimension of the study, which is mandatory to achieve a meaningful result. On the other hand, non-commercial trials, that are initiated by the investigators, capacitate them, contributing to a general capacity for the research, clinical study and impact.

Objectives: This study aims to identify the scientific impact of the commercial and non-commercial clinical trials with Portuguese institutions as sponsors or/and participating country.

Design and Methods: A systematic search of trial registrations from 01/10/2004 to 30/09/2018 – using four clinical trials registries (CTRs) – was carried out to identify the interventional clinical trials with Portugal as sponsor or participating country. Information about the sponsor, funders, intervention type, and therapeutic area was obtained from each CTR. Every completed study was screened for publications and data collected from databases were complemented with data contained in publications. The impact factor of each journal and quartile in the respective publication year was also registered.

Outcome: For the first time, the scientific impact and characteristics of both commercial and non-commercial clinical trials implemented in Portugal were assessed considering four different clinical trials registries and the information gathered from publications of completed studies. It was a great achievement conducting this analysis on a high number of clinical trials, implicating an exhaustive methodological approach.

Results: The number of commercial clinical trials (n= 1402) registered was higher than the non-commercial clinical trials (n= 339). A total of 970 commercial clinical trials were completed and only 280 (28.87%) were published, from those, only 24 (8.57%) had Portuguese authorship. On the other hand, 170 non-commercial clinical trials were completed studies, 54 (31.76%) were published and 38 (70.37%) of them had Portuguese authorship. Oncology is the therapeutic area with more commercial studies published (20.71%) and chemical drugs the most applied interventions (65.71%). Considering the publications of the non-commercial clinical

trials, Cardiology/Vascular Diseases is the main area of concern (16.67%) and behavioral interventions the most studied (31.48%). Eighty-three percent of the clinical trials published were sponsored by the pharmaceutical industry. Nevertheless, the publications with Portuguese authorship (43.55%) had universities as lead sponsors. Commercial clinical trials took 1.82 ± 0.10 years to publish their results while non-commercial trials took 2.13 ± 0.21 years. These results were not statistically different ($p > 0.05$). Commercial clinical trials were published in journals with a higher mean impact factor than non-commercial clinical trials (21.65 ± 1.33 and 15.63 ± 3.27, respectively; $p < 0.05$). Also, commercial clinical trials with Portuguese authors have a mean impact factor higher than non-commercial trials (17.09 ± 4.80 and 6.42 ± 1.93, respectively; $p < 0.05$).

Conclusions: In this study, we conclude that commercial and non-commercial trials are published in similar percentages (around 30%). Portuguese authorship in non-commercial clinical trials has a higher percentage of publications when compared to those from commercial clinical trials (70.37% vs 8.57%). Oncology is the therapeutic area of higher number of registered trials, but it is not the most target one in the publications of non-commercial clinical trials. The mean time from the end of a clinical trial to the publication of its results is around 2 years both for commercial and non-commercial clinical trials. On average, commercial trials are published in journals with higher Impact Factors, when compared to those from non-commercial trials. A higher difference is observed in publications with Portuguese authors (17.09 vs 6.42).

The scientific output of this work so far:

- Preliminary conclusions from part of this research project were previously presented as an oral communication (selected by abstract) at the Portuguese Society of Pharmacology annual meeting (February 2019) in Porto entitled: The scientific impact of investigator-initiated clinical trials in Portuguese institutions: a systematic search in clinical trials databases.
- By invitation, the same work was presented in a class of the "Clinical Trials Monitor Career Initiation Course", which was held at the Faculty of Pharmacy of the University of Porto (February 2019).

KEYWORDS

Clinical trials; Commercial trials; Non-Commercial Clinical Trials; Clinical Trials Registries; Scientific Impact

RESUMO

Introdução: A investigação clínica ou estudos clínicos, que faz parte do ramo das ciências da saúde, é qualquer tipo de investigação médica que envolva participantes humanos. Estes estudos têm como objetivo primário responder a questões científicas específicas e produzir conhecimento valioso para a compreensão de doenças humanas, prevenção ou tratamento de doenças e promoção da saúde.

Os ensaios clínicos são muito importantes uma vez que providenciam as ferramentas essenciais para traduzir descobertas científicas em terapias inovadoras, permitem a comercialização de novos fármacos e têm um papel crucial na resposta a questões médicas e científicas. Estes estudos podem ser divididos em ensaios comerciais (promovidos por organizações comerciais como as indústrias farmacêuticas) e ensaios não comerciais (geralmente promovidos por uma organização sem fins lucrativos). Nos ensaios comerciais, os investigadores limitam-se a executar um protocolo definido pela indústria, capacitando o investigador para a execução e prestação de serviços. Por outro lado, nos ensaios não comerciais, os investigadores ou a instituição são os responsáveis pelo desenho e execução do protocolo do ensaio clínico, contribuindo para uma capacitação geral de investigação, de estudo clínico e de impacto científico.

De facto, hoje em dia a indústria farmacêutica é a principal promotora de ensaios clínicos em todo mundo apesar do seu foco primário se prender com a comercialização das suas terapias. A proporção de ensaios clínicos não comerciais (ou seja, ensaios clínicos da iniciativa do investigador) é consideravelmente inferior. Ainda assim, a informação proveniente destes estudos é extremamente importante para o bem-estar geral da sociedade, uma vez que é imparcial e não existe nenhum interesse comercial associado.

Considerando o impacto científico que ambos os tipos de ensaios clínicos promovem, existem ainda algumas divergências. Os estudos comerciais são frequentemente publicados em jornais com fatores de impacto elevados devido à grande complexidade e dimensão dos estudos que é essencial para atingir resultados relevantes e significativos. Por outro lado, os ensaios não comerciais são normalmente ensaios de menores dimensões, com restrições financeiras e cujos resultados são publicados em artigos científicos ou são apresentados em conferências, sendo associados a fatores de impacto inferiores.

Objetivos: Este estudo tem como objetivo principal identificar o impacto científico dos ensaios comerciais e não comerciais que tenham instituições Portuguesas como promotores e /ou Portugal como país participante. Os objetivos secundários prendem-se com comparação nos ensaios comerciais e não comerciais relativamente à: identificação de autores portugueses nas publicações, verificação das áreas terapêuticas de maior interesse onde existe um maior número de publicações e também no tempo médio que decorre desde o término de um ensaio até a publicação dos seus resultados.

Metodologia: Uma pesquisa sistemática desde 01/10/2004 a 30/09/2018 foi realizada utilizando quatro plataformas de registo online de ensaios clínicos – Clinicaltrials.gov, EU-CTR, ISRCTN, ANZCTR - para identificar os ensaios clínicos a incluir neste trabalho de investigação. Os três critérios de inclusão utilizados foram: ter como país participante Portugal, ser um estudo de intervenção e ter data de início entre 01/10/2004 a 30/09/2018. A informação relativa ao número de identificação do ensaio, promotor, financiador, tipo de intervenção, área terapêutica, data de início e título do estudo foi obtida através das plataformas de registo referidas acima. A classificação relativa à natureza dos ensaios clínicos (comerciais ou não comerciais) foi feita manualmente, através do nome do promotor do ensaio, uma vez que os registos de ensaios clínicos não possuem essa informação (à exceção da EU-CTR).

Para selecionar as publicações, apenas foram considerados os ensaios completos. Para além disso, só a primeira publicação de resultados após o término dos ensaios é que foi considerada. Tendo em conta apenas os ensaios completos, as possíveis publicações foram procuradas através do número de identificação dos ensaios numa pesquisa na base de dados MEDLINE (PubMed). A informação recolhida foi utilizada para complementar a informação obtida nos registos online. Em cada publicação, o ano de publicação, o jornal onde o artigo foi publicado, o fator de impacto e o percentil do respetivo ano de publicação foram registados.

Para analisar toda a informação obtida, foi efetuada uma análise descritiva dos resultados. Quando adequado, foi realizada uma análise estatística. As amostras utilizadas não seguiam uma distribuição normal pelo que foi utilizado um teste não paramétrico (teste de Mann-Withney para amostras independentes) com uma confiança de 95%.

Relevância: Pela primeira vez, foi conduzido um estudo relativo ao impacto científico com informação detalhada das características dos ensaios comerciais e não comerciais em Portugal utilizando quatro plataformas de registos clínicos e cruzando essa informação com as

publicações dos ensaios completos. Foi uma grande conquista conduzir essa análise num número tão elevado de ensaios clínicos, implicando uma abordagem metodológica exaustiva. A relevância de aceder ao impacto científico de ensaios clínicos comerciais e não comerciais de maneira comparativa é muito significativa. Não há dúvida de que as informações fornecidas pelos ensaios da iniciativa do investigador são extremamente importantes, uma vez que os dados clínicos gerados poderão ter um grande impacto nas políticas de saúde na Europa e inovar áreas clínicas que são desconsideradas pela indústria devido à sua lucratividade muito baixa ou inexistente. Além disso, ainda existem poucos ensaios não comerciais publicados em jornais científicos com fator de impacto mais alto quando comparados com os comerciais havendo uma necessidade urgente de entender e superar esse revés.

Resultados: Foram identificados um maior número de ensaios clínicos comerciais registados (n= 1402) em comparação com o número de ensaios não comerciais (n= 339). Dentro dos ensaios comerciais, 970 estão completos e apenas 280 (28.87%) publicados, dos quais, 24 (8.57) têm autoria portuguesa. Por outro lado, 170 ensaios não comerciais estão completos, dos quais 54 (31.76%) estão publicados e 38 (70.37%) têm autoria portuguesa. A área oncológica é a área terapêutica mais estudada nos ensaios comerciais publicados (20.71%) e os fármacos químicos as intervenções mais estudadas (65.71%). Em relação aos ensaios não comerciais publicados, a cardiologia é a área de terapêutica de maior interesse (16.67%) e as intervenções comportamentais as mais aplicadas (31.48%). Relativamente à média dos fatores de impacto dos jornais onde os resultados dos ensaios são publicados, esta é significativamente superior ($p < 0.05$) nos os ensaios comerciais (21.65 ± 1.33) quando comparada com a média dos fatores de impacto dos ensaios não comerciais (15.63 ± 3.27). Para além disso, os ensaios comerciais com autores portugueses têm uma média de fatores de impacto de 17.09 ± 4.80 enquanto que os não comerciais apenas têm uma média de 6.42 ± 1.93 ($p < 0.05$). Quando falamos do tempo gasto desde o término do ensaio clínico até à publicação dos seus resultados na literatura científica, não existem diferenças significativas sendo que o tempo gasto para a publicação dos resultados é cerca de dois anos para os ensaios comerciais e não comerciais ($p > 0.05$).

Conclusões: Quando comparados com os ensaios comerciais, os ensaios não comerciais têm uma maior percentagem de publicações e de publicações com autores portugueses. No entanto, é claro que os promotores comerciais publicam mais frequentemente em jornais com fatores de impacto e quartis mais elevados sobre áreas da medicina que são consideradas as mais prevalentes e incidentes no mundo. Os ensaios não comerciais dedicam-se sobretudo a

estudos de cardiologia. Relativamente ao tempo médio para a publicação dos resultados, este é semelhante tanto para os ensaios comerciais como não comerciais (aproximadamente 2 anos). Ao comparar as médias dos fatores de impacto dos ensaios comerciais e não comerciais, existem algumas divergências significativas: embora os ensaios clínicos comercias sejam publicados em jornais com fatores de impacto superiores, a maioria destas publicações não tem autores portugueses, ao contrário do que se passa com a publicação de estudos não comercias. Será relevante, no futuro, desenvolver estratégias nacionais que passem pela inclusão de investigadores portugueses em estudos comercias desde uma fase inicial de preparação do estudo, bem como estimular a realização de estudos não comerciais com financiamento substancial para aumentar o impacto científico dos mesmos.

Produção científica deste trabalho até à data:

- As conclusões preliminares de parte deste projeto foram apresentadas anteriormente, numa comunicação oral (selecionada pelo Resumo) na reunião anual da Sociedade Portuguesa de Farmacologia (fevereiro 2019) no Porto, intitulada: O impacto científico dos ensaios clínicos iniciados por investigadores em instituições portuguesas: uma pesquisa sistemática em plataformas online de ensaios clínicos.

- Por convite, o mesmo trabalho foi apresentado numa aula do "Curso de Iniciação à Carreira de Monitor de Ensaios Clínicos", que se realizou na Faculdade de Farmácia da Universidade do Porto (fevereiro 2019).

PALAVRAS CHAVE

Ensaios Clínicos; Ensaios Comerciais; Ensaios Não Comerciais; Registos de Ensaios Clínicos; Impacto Científico

ACKNOWLEDGMENTS

Gostaria de agradecer a todos que, durante este ano estiveram de alguma forma presentes e ajudaram-me em todo o processo da elaboração da dissertação, que me apoiaram e incentivaram a dedicar-me a este trabalho tão marcante e exigente.

Quero deixar um especial agradecimento à minha orientadora, Catarina Madeira, por ter aceite orientar a minha tese, por me ter recebido de braços abertos, apoiado e ajudado em todos os pequenos passos que dei e por me incentivar a fazer um trabalho de qualidade. A sua genuína paixão pela ciência aliada com o seu caráter humano, permitiram que ao longo deste ano de trabalho me sentisse genuinamente bem orientada e que pudesse sempre contar com a sua disponibilidade e preocupação. Obrigada por toda a partilha de conhecimento, por todas as correções e por todo o apoio. Sei que não poderia ter escolhido melhor profissional e melhor pessoa para me acompanhar nesta fase tão importante.

Ao professor Helder Mota-Filipe, obrigada por se ter disponibilizado em coorientar a minha tese e fazer parte deste trabalho. Obrigada pelas suas orientações, conhecimento e por todo o apoio que me deu. Apesar do tempo limitado do professor, foi uma peça essencial para que o presente trabalho fosse concluído.

Não poderia deixar de agradecer à Dr. Joana Batuca que, em conjunto com a minha orientadora, formaram uma equipa de apoio incondicional durante o trabalho feito ao longo do ano. Obrigada por me ter recebido de braços abertos e me ter ajudado como uma orientadora. Obrigada pela alegria e boa disposição, pela disponibilidade e por todo o apoio.

À professora Emília Monteiro devo deixar um agradecimento por me ter acolhido no seu grupo. A sua supervisão e apoio foram essenciais para que me sentisse confortável com todo o projeto e para chegar até aqui. Para além disso devo expressar o meu profundo agradecimento pela oportunidade dada, em conjunto com o grupo PtCRIN, em participar na reunião anual da Sociedade Portuguesa de Farmacologia, que foi uma experiência única, e espero que a primeira de muitas.

À Tânia, à Sara, ao Rafael, à Daniela e à Inês, pela paciência, pelo apoio, pela amizade, pelo companheirismo, pelas risadas, pelos desvaneios, pelas sessões de escrita. Obrigada por me acompanharem nesta fase que (ainda) partilhamos, e pela entreajuda que me deu força para

continuar. Especialmente a ti, Tânia, que estiveste sempre lá e que me acompanhaste desde o início. Obrigada pelos encontros na biblioteca, pelas brincadeiras, pelas risadas, por stressarmos juntas e por termos chegado aqui juntas.

À Carolina, à Mariana, à Joana, à Violeta e à Margarida, por terem acreditado mais do que eu e por terem aturado os meus desânimos. Obrigada por terem estado sempre lá e terem-me encorajado a superar-me.

Ao Rui, por todo o amor, dedicação, paciência e presença constante neste trabalho. Obrigada por me fazeres lembrar todos os dias o porquê de estar aqui e de querer continuar. Obrigada por me desafiares a ser melhor a todos os níveis. Obrigada por todas as palavras e todos os momentos silenciosos em que senti o teu apoio. Obrigada por acreditares mais do que eu e por me incentivares a ir atrás dos meus sonhos. Obrigada por tudo.

Aos meus familiares, em especial aos meus pais e à minha tia, um enorme obrigada. Pela paciência, pelo apoio incondicional, mas acima de tudo por me lembrarem das minhas responsabilidades.

Devo ainda agradecer a todos aqueles que direta ou indiretamente contribuíram para que este projeto fosse possível.

Great things are not done by one person.

They're done by a team of people.

- Steve Jobs

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ABBREVIATIONS

AIBILI	Association for Innovation and Biomedical Research on Light and Image
ANZCTR	Australian New Zealand Clinical Trials Registry
CEIC	National Commission of Ethics for Clinical Research
CNPD	National Commission for Data Protection
CRC	Clinical Research Centers
CRO	Contract Research Organization
CTR	Clinical Trials Registries
CTU	Clinical Trials Units
DOI	Digital Object Identifier
DPO	Data Protection Officer
ECRIN	European Clinical Research Infrastructure Network
EEA	European Economic Area
EMA	European Medicines Agency
EORCT	European Organisation for Research and Treatment of Cancer
EU	European Union
EUA	European Economic Area
EU-CTR	EU Clinical Trials Register
EUDAMED	European Databank on Medical Devices
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
ICTRP	International Clinical Trials Registry Platform
ID	Identification
IICT	Investigator-Initiated Clinical Trials
IF	Impact Factor
INFARMED	National Authority of Medicines and Health Products
ISI	Institute for Scientific Information
ISRCTN	International Standard Randomised Controlled Trial Number Register
JIF	Journal Impact Factor

NMS	Nova Medical School
PT	Portugal
PtCRIN	Portuguese Clinical Research Infrastructure Network
Q	Quartile
Q1	Quartile 1
Q2	Quartile 2
Q3	Quartile 3
Q4	Quartile 4
SPSS	Statistical Package of Social Science
UK	United Kingdom
US	United States
USA	United States of America
US-NIH	United States National Institutes of Health
WHO	World Health Organization

1. INTRODUCTION

1.1 History of Clinical Trials

The history of "Clinical Research" covers a wide variety of terms: ethical, scientific, and regulatory standards. From ancient medical studies to the concept known nowadays, there has been a great evolution and long journey.

The first documented Clinical Trial is recorded in the "Book of Daniel" which belongs to The Bible, where a group of children was ordered to be fed a strict diet of meat and wine [1]. However, within the group, several youths of royal blood and vegetable lovers objected and took a different diet. After three years, when the experiment ended, the vegetable lovers appeared better nourished than the meat-eaters [1]. This study was not conducted by a medical doctor or a scientist, but by a military leader – King Nebuchadnezzar – and the participants involved were not volunteers [1].

Around the 10th century, Avicenna wrote the "Canon of Medicine" describing some rules for the testing of drugs [2]. Within the encyclopedia, he suggested that the drug must be pure and used on a "simple" disease, tested on at least two different types of diseases and that the drug should be tested in animals first, thereafter in humans, as the effects in animals and humans may not be the same [2]. This step of the clinical research emphasizes some concerns in testing drugs in human beings and lays down the need for effectiveness and comparative trials.

It was only in 1747 that the firstly considered modern clinical trial was introduced. James Lind was a physician that conducted a study regarding the high mortality of scurvy, and his vivid description of the trial covers the essential elements of a controlled trial [3]. The participants should be followed closely by the physician and the cases of the disease were as similar as possible. A few years later the word "placebo" appeared in the medical literature, but it was just in 1863 that the physician Austin Flint planned the first clinical study using the principle of placebo, where he compared a dummy remedy to a previously considered active treatment.

Over the years, as the discipline of controlled trials grew in sophistication and influence, the first double-blind controlled trial took place (1943) followed by the first randomized curative trial (1946), congregating into the actual concept of clinical studies. Following the evolution of clinical research, the ethical and regulatory frameworks also progressed throughout

the decades. Its origin goes back to the ancient Hippocratic Oath, which stipulates the prime duty of a physician: to avoid harming the patient. Despite that, the practical use of the oath was not widely respected in human experimentations and the majority of advances in protection for human subjects have been a response to human abuses [2].

It was only in 1900 that the concept of consent for participation in clinical research was created and in 1947, the first International Guidance on the ethics on medical research involving subjects -Nuremberg Code- was formulated by layers, following the Nazis abuses during the second world war. The Nuremberg Code highlighted the elementality of voluntariness [4]. In the early '60s, the Helsinki Declaration was written by medical doctors, from different Medical Associations from the World and established specific guidelines on the use of human subjects in medical research. Every few years it is adjusted in accordance with the evolution of clinical research.

The Good Clinical Practice (GCP) which has become the universal standard for the ethical conduct of clinical trials was published in 1996 by the International Conference on Harmonization [5]. In this guideline, we can find all the ethical and scientific quality standards for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible [5].

In parallel to the ethical guidelines, government authorities started recognizing the need for regulation and controlling medical therapies. The US (United States) Food and Drug Administration (FDA) was founded in 1862 as the scientific institution and law enforcement organization of the United States. In the European Union (EU), the competent authority for the regulation of the clinical trials is the European Medicines Agency (EMA) that was founded in 1995.

The concept of Clinical Research has reached a consensual perception and it is subcategorized in Clinical Trials (trials with intervention) and Observational Trials (trials without intervention). Nowadays, it is imperative that all the participants are volunteers and sign the informed consent, that the GCP are strictly respected and all regulatory affairs assessed. Nevertheless, as the technologies and scientific disciplines become part of the drug

development process, the regulatory and ethical cornerstones will continue to evolve to new concepts and modulated terms.

1.2 Definition of Clinical Studies

A Clinical Study or a Clinical Research, part of the field of healthcare sciences, is any type of medical research that involves human volunteers (also called participants). These studies intend to answer specific scientific questions and produce valuable knowledge for understanding human diseases, preventing and treating illness, and promoting health. Clinical Research embraces a range of studies engaging interactions with patients, diagnostic clinical materials or data, or populations in any of the following categories [6]:

1. Disease mechanisms (etiopathogenesis);
2. Bi-directional integrative (translational) research;
3. Clinical knowledge, detection, diagnosis and natural history of the disease;
4. Therapeutic interventions including development and clinical trials of chemical drugs, biologics, devices, and instruments;
5. Prevention (primary and secondary) and health promotion;
6. Behavioral research;
7. Health services research, including outcomes, and cost-effectiveness;
8. Epidemiology;
9. Community-based and managed care-based trials.

Clinical studies are the cornerstones of clinical patient-oriented research as they provide the tools for translating basic scientific discoveries into innovative therapies, have the necessary data upon the commercialization of a new drug and can play a key role in answering important medical and scientific questions [7], [8]. These studies are crucial to ensure patient safety and efficient patient care, accelerating the accrual of patients, especially for uncommon diseases [9]. As an important part of the patient-oriented study, clinical trials undergo a strict regulatory process assessed by the regulatory entities and must follow the GCP statements.

There are two main types of clinical studies: Observational trials and Clinical trials (also called interventional or experimental studies).

1.2.1 Observational and Interventional Studies

The field of Clinical research can be divided into Observational Studies or Interventional Studies (also known as Clinical Trials).

The term "Observational Trial" is used to describe clinical research studies where the people involved are observed in normal settings. This means that no change in daily routine is applied to the participants. Investigators gather information, assess health outcomes, group the volunteers according to broad characteristics, and compare changes over time. Participants may be receiving interventions (such as medicinal products or devices) or procedures as part of their medical care routine but they are not assigned to a specific intervention by the investigator (as in clinical trials). This type of research is mainly used in fields such as epidemiology, social sciences, and psychology and may help to identify new possibilities for clinical trials.

On the other hand, an experimental/interventional study, also called clinical trial, according to the World Health Organization (WHO) "is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes" [10]. This includes testing not only new medicines but also new therapies, devices, diagnostic techniques, and surgical procedures, as well as optimizing existing medical products to uphold better health and welfare. Some clinical trials may also compare a new medical approach to a standard one, to a placebo or to no intervention, as well as compare interventions that are already available with each other.

At a national level, the law 21/2014 from 16th of April, states the current definitions, duties, and rights of all the intervenient and concepts related to clinical research [10]. This law revokes the previous law 46/2004 from 19th August, which was the first law approved in Portugal applicable to the conduct of clinical trials with medicinal products for human use. Posteriorly to 2014, a new law emerged to modify the law 21/2014 to establish the conditions under which monitors, auditors, and inspectors may access the register of participants in clinical studies. According to the Portuguese Law for Clinical Research, the term clinical trial is only used in interventions with medicines, but in this work, we will consider a broad definition, including all the intervention studies.

Nevertheless, within both main categories of Interventional and Observational studies, the clinical investigation can be divided into further types as shown in Figure 1 [11]. For experimental/interventional studies, they can be divided into Randomized controlled trials (if

any allocation scheme was used) or Non-Randomized controlled trials. For observational studies, the first division is based on whether the study has a comparison or control group. If not, the study is classified as a descriptive study. If so, it is considered an analytical study that can be divided by the temporal direction of the trial. If the study determines both exposures and outcomes at one time point, it is termed cross-sectional; If the study begins with an exposure follows participants for a few years to measure outcomes, then it is deemed a cohort study; and if the analytical study begins with an outcome and looks back in time for an exposure, then the study is a case-control study.

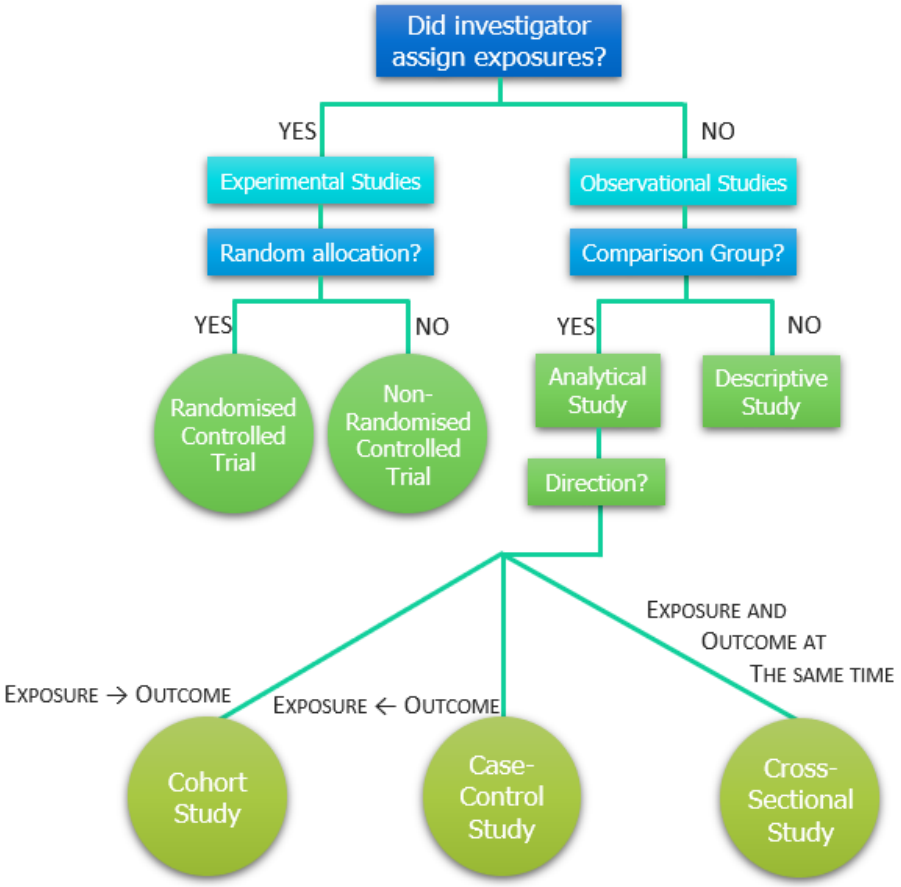

Figure 1: Algorithm for classification of types of clinical research. Adapted from reference [11].

It is important to understand that each type of clinical study is associated with medical evidence. There are several principles that contribute to the formulation of a hierarchy pyramid of evidence in clinical investigation. From the bottom to the top of the pyramid there is an increase in evidence, regulations, the complexity of the study design, human resources, among others. There are various versions of the evidence pyramid but all of them focus on showing weaker studies on the bottom and systematic reviews and meta-analysis at the top (Figure 2) [12]. Throughout the years several counterarguments have been raised and the traditional

pyramid was deemed too simplistic. Although there are some proposals, there is still no consensus, so the traditional pyramid is still considered.

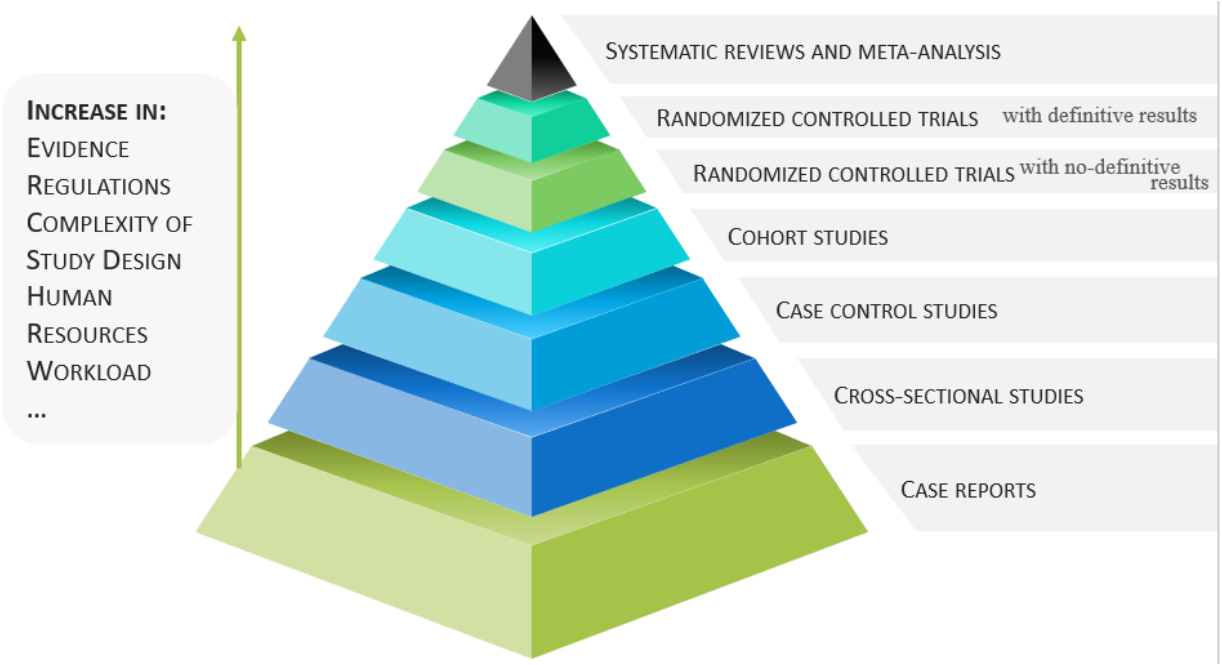

Figure 2: The hierarchy of evidence: types of clinical studies impact. Adapted from reference [13]**.**

1.2.2 Intervention with Medicines

Within the interventional trials, the most commonly used are the interventions with medicines that include both chemical and biological drugs. Although there are clinical trials for other interventions, the general road to drug development and approval has been defined and regulated by the US FDA and the European Parliament with EMA.

Interventional trials with medicines happen in several phases during which different questions are asked. Each phase builds on the results of previous phases and knowing the phase of the clinical trial can give some idea about how much is known about the treatment studied. The Clinical Trials can be typically divided into four phases: Phase I, II, III and IV [14], [15]. Nevertheless, with innovative medicines, first-in-human trials – Phase 0 or Early Phase I – can also be used to evaluate the safety of a microdose in humans for the first time once there was an ascending existence of adverse events in Phase I trials [16], [17].

The **Pre-clinical phase**, as the name suggests, characterizes the last studies done in the laboratory before applying the therapies in humans. Preclinical research seeks to obtain preliminary efficacy, toxicity, and pharmacokinetic information and only if these studies show

viable and favorable results can they be approved for use in humans [18]. These studies are the primary way to investigate if a specific intervention has scientific merit for further development in Clinical Trials [19].

Early phase 1 studies is the newly term given to the first-in-human clinical trials [20], [21]. This exploratory trial phase involves very limited human exposure and has no therapeutic or diagnostic intent. Studies are conducted prior to the traditional dose-escalation, safety, and tolerance trials and are commonly known as microdose or screening studies. Once they are part of the first contact of a drug with humans, the enrollment is approximately 10 to 15 subjects and the drug is given only for a short period of time (±7 days). In this phase, researchers find out whether the drugs act as expected and if it is not the case, the drug does not proceed to the next phase and more preclinical studies are required [17].

Phase I trials are also known as "dose-escalation" or "human pharmacology" studies. These studies allow investigators to analyze the effectiveness, pharmacokinetics, pharmacodynamics, and tolerability of the experimental drug in terms of side effects related to dose [14], [22]. The trials may be performed in healthy volunteers and/or in patients and tests are made in a small group of people (20 to 80 individuals) [21].

Phase II trials are performed on larger groups of participants who are living with the condition that the new medicine is meant to treat. These are the first controlled clinical studies designed to assess the efficacy of a drug and evaluate the risks and side effects [22]. Phase II trials are also referred to as "therapeutic exploratory" trials where the patients are closely followed-up and investigators try to answer questions essential for the planning of larger phase III trials (determination of optimal doses, dose frequencies and administration routines) [14].

EMA and FDA describe **Phase III** trials as the expanded, controlled and uncontrolled studies performed after some evidence has been found to suggest the efficacy of an experimental therapy. This stage of drug assessment is also referred to as "therapeutic confirmatory", "comparative efficacy" or "pivotal trial" and is conducted on a broader target population (300 to 3000 volunteers who have the disease or condition) [15]. The main purpose of phase III trials is to evaluate how the new therapeutic works in terms of efficacy and to identify and estimate the incidence of common adverse reactions. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions. At the

end of this phase, especially in commercial studies, a marketing authorization for the new medicine or new indication is requested.

Phase IV clinical trials are also known as post-marketing surveillance trials once they only occur after the therapy approval by FDA or EMA [14], [15]. This phase involves thousands of participants and the investigators use these studies to get more information upon the medication's long-term safety, effectiveness, and pharmacovigilance. Phase IV studies may be required by regulatory authorities (e.g. change in labeling, risk management/minimization action plan) or may be undertaken by the sponsoring company for competitive purposes or other reasons [5].

There are several differences between all the phases of the clinical trials regarding the purpose, length of study and number of participants. Table 1 summarizes all the differences described above for the phases of the clinical trials.

Table 1: Comparison of the different phases of a clinical trial with medicines concerning the purpose, length of study, number of participants and estimated percentage of approval to the next phase.

	Purpose	***Length of Study***	***Study Participants***	***Percentage of approval to next phase*** [23]
Phase I	Safety and Dosage	Several Months	20 to 80 healthy volunteers or people with the disease	75%
Phase II	Efficacy and Side Effects	Several months to 2 years	Up to several hundred people with the disease	50%
Phase III	Efficacy and Monitoring of Adverse Reactions	1 to 4 years	300 to 3000 volunteers who have the disease	59%
Phase IV	Safety and Efficacy	Several years	Several thousand volunteers who have the disease	88%

1.2.3 Intervention with Medical Devices

Medical devices have become a prominent and substantial part of the clinical practice. Throughout the years, as the technologies and sciences are in constant progress, the areas of medicine and healthcare have been experiencing great improvements. Around the world there are subtle differences in wording that prevent a global harmonization of the definition of a medical device, thus the appropriate definition of a medical device depends on the region.

According to Article 1 of Council Directive 93/42/EEC, medical devices are any instruments, apparatus, machine appliance, implant or software intended to be used alone or in combination in human beings [24]. The widespread medical purposes of these devices rely on diagnosis, prevention, monitoring, treatment, alleviation of disease, replacement or other similar intends not mentioned above.

The classification of medical devices in the EU is based on rules that involve the medical device's duration of body contact, invasive character, use of an energy source, the effect on the central circulation or nervous system, diagnostic impact, or incorporation of a medicinal product [24]. There are four classes, ranging from minimal to substantial risk: Class I; Class IIa, Class IIb, and Class III.

Medical device trials are different from the drug trials in those only patients with the condition which the device is designed to treat are involved. Besides that, they are mostly conducted in a smaller population and the number of subjects needed to show safety and effectiveness is often only one or two hundred, rather than a thousand needed for drug trials. Nevertheless, such as in the clinical trials with medicines, trials with medical devices are also divided into phases that lead to approval. There are only three phases: Pilot study, Pivotal study, and Post-Approval Study.

The Pilot studies, also known as exploratory or Feasibility study, are conducted in the early stages of device development. They are used to establish preliminary safety and effectiveness of the device and design the next stage of the trial. As the first contact of the device with humans, only 10 to 30 subjects with the condition or disease are enrolled.

The Pivotal studies are performed to demonstrate that the device is safe and effective for specific use within a defined patient population. These studies enroll 150 to 300 subjects with

the disease or condition studied and the results are used to gain regulatory approval to market the device.

The Post-Approval Studies or Postmarket Studies run either as a condition of approval to meet a business objective, post-market studies are similar to Phase IV of clinical drug trials since the goal is to better understand long-term effectiveness of the device and potential adverse events associated with the use of the device.

As a new intervention on the wide history of clinical research, medical devices undergo a restrict and distinct regulatory process to demonstrate that they meet legal requirements to ensure they are safe and perform as intended. At the European level, the core legal framework consists of three directives that set the rights and duties of the investigators, sponsors and the National Competent Authority for conducting a medical device clinical trial.

In fact, as a continuous work-in-progress in the clinical research field, the three directives are currently undergoing an adaption process. The Directive 90/385/EEC regarding active implantable medical devices and Directive 93/42/EEC regarding medical devices will be replaced by Article 32 of Medical Device Regulation 2017/745 in May 2020. As for the Directive 98/79/EC regarding in vitro diagnostic medical devices, this will be replaced by the Medical Device Regulation 2017/746 in 2022. These modifications emphasize the security approach based on the life cycle of the medical devices supported by clinical data [25]. At the national level the clinical trials upon medical devices undergo a specific regulation established on the Portuguese Law for Clinical Research 21/2014 from 16th of April and the Law 145/2009 from 17th of June that states the rules of investigation, manufacture, commercialization, monitoring, and publicity of the medical devices. Besides that, there must be followed GCP procedures under the standard EN ISO 14155 and relevant scientific guidelines provided by the European Commission [25].

There are several Clinical Trials Registries (CTRs) including the European (EU-CTR), which is open to a public registry of clinical trials on medicinal products (see section **1.5**). Upon medical devices, the European Databank on Medical Devices (EUDAMED) is a portal that is used as a central repository for information exchange between the competent authorities and the European Commission in accordance with the Directives of Medical Devices. This databank was created in 2011 to strengthen the monitoring and transparency of the usage of commercialized medical devices. As of today, the general public does not have access to this

database. Even though a new EUDAMED portal is being developed and it will include more information upon the medical devices including their clinical evaluation; the registry of the clinical trials; and open assess of part of the information to the public. It is expected that the new portal will be available on September 2021 and, just as it happened with the clinical trials on medicines when the CTRs where created, it is expected that the number of clinical trials with medical devices increases considerably.

1.2.4 Other Interventional Studies

In addition to the interventions mentioned above, there are also other types of interventional studies. Medical procedures like surgeries, rehabilitation procedures, behavior interventions, nutrition, diagnostic tests, and radiation therapies may also be studied in a clinical trial. Although these are not the conventional therapies used in clinical trials, they seek to address, reduce or stabilize an individual's health problem (symptom or disease) or to eliminate a modifiable risk factor (prodrome or high-risk disease-causing behavior). Besides that, these interventions aim at enhancing the effects of conventional treatments, are often used as combined therapies.

1.3 Clinical Trials Stakeholders

In order to perform well established, efficient and knowledgeable clinical study it's imperative to have a healthy dynamic between the clinical trials players. The main stakeholders involved in the development of a clinical trial, mainly when involving medicines or medical devices, are the Sponsor; Funder; Competent authorities and Ethical Committees; Health Units; Supporting Infrastructures; Investigation team; and the study participants. Each one has a well-defined role and due to the great demand and complexity associated with the process of research and development of new medicines or medical devices, mutual support between the stakeholders is crucial.

1.3.1 Sponsors and Funders

The **Sponsor** of a clinical trial is "an individual, company, institution or organization which takes responsibility for the initiation, the management and for setting up the financing of the clinical trial" [10]. As the responsible for initiating the clinical trial, the sponsor is the identity who must be in permanent contact with all the other stakeholders. They are responsible for recruiting the financial support, require to the competent authority the authorization for

conducting the clinical trial, contact the health units and ensure compliance with duties and laws [10], [26].

The **Sponsor** may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization, depending on if a trial is commercial or non-commercial (see section **1.4**). The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator as in some Non-Commercial Trials. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, and the employees are investigators [27].

The **Funder** of a clinical trial is the entity providing financial support for the study. This organization may be a for-profit organization or a non-profit one, depending on how they manage the profits. In a non-profit organization, the society comes first and in a for-profit-organization the commercial motives are the firstly assessed.

Usually, the terms "**Sponsor**" and "**Funder**" of the clinical trials are mistaken and considered as one. In fact, the Sponsor and Funder of a clinical trial may be the same. In commercial clinical trials, the funding source is the sponsor, whereas in non-commercial trials the sponsor might not be the funder. According to the European Regulation for clinical research (Regulation 536/2014EC), the funds for these non-commercial trials might come partly or entirely from public funds or charities and the sponsor is generally the organization that receives the funds [28].

1.3.2 Competent Authorities and Ethical Committees

Around the world, there are several competent authorities that have their own regulations upon the correspondent region or country. The FDA it the US authority upon drug clinical trials and EMA is the authority in the EU. Their main responsibility is to review and approving clinical trials and ensure that the clinical trials comply with the national regulations of a country and international guidelines.

In Portugal there are specific organizations that are required for the conduction of a clinical trial and work closely to EMA as a member of the EU:

- **INFARMED** (National Authority of Medicines and Health Products) is the competent authority primarily responsible for the evaluation, regulation, supervision, and

authorization of medicines for human use, as well as other health products like medical devices, homeopathic products or cosmetics.

- **CEIC** (National Commission of Ethics for Clinical Research) is an independent organization consisting of health-related individuals whose mission is to protect the rights, safety, and well-being of the participants in clinical trials through the issuance of an opinion on ethical and research protocols that are submitted. This commission also has to ensure that the GCP is fulfilled.
- **CNPD** (National Commission for Data Protection) is an independent entity endowed with the power to supervise and monitor compliance with laws and regulations on the protection of personal data in strict respect for human rights and the freedoms and guarantees enshrined in the constitution. According to the New Regulation on Data Protection, CNPD will only act as a control/auditor body and a Data Protection Officer (DPO) in each health institution is responsible for assuring the Data Protection of all the clinical trial participants [29].

1.3.3 Health Units

For conducting a clinical trial, it is imperative that recruiting centers are involved. These centers also called Clinical Research Centers (CRC), are any designated medical facility used to conduct the clinical study, such as a hospital or medical clinic. They must provide optimal settings for medical investigators to conduct safe and controlled trials. Besides that, they also provide the necessary infrastructure and help investigators facilitate the day-to-day research process and assist the research subjects in a supportive and efficient environment.

1.3.4 Supporting Infrastructures

The outsourcing of tasks related to clinical research has increased substantially over the past decades. In fact, nowadays there are thousands of service provider organizations worldwide [30]. There are two principal types of supporting infrastructures: Contract Research Organization (CRO) or Clinical Trials Units (CTU). CROs are profit organizations and CTUs are generally hosted by non-profit organizations [26]. These organizations are independent from sponsors providing services on clinical trials. The scope of action of these infrastructures is diversified has they can ensure all development activities or only one part. The services are related to the trial management, clinical site selection and contracting, drug management, data management and monitoring, statistical analysis and medical reporting. Furthermore, these

supporting organizations may also manage the regulatory and ethical applications needed for the approval and conducting of the clinical study. In the case of non-commercial studies, CTUs may also support the investigators in the study design and preparation of the protocol, statistic plan, among others.

The European Clinical Research Infrastructure Network (ECRIN) is listed as a non-profit intergovernmental organization that supports the conduct of clinical trials in Europe. It works with European Correspondents across Europe, CTUs and international stakeholders involved in clinical research. Portugal has signed ECRIN statutes as a Member Country and the Portuguese Clinical Research Infrastructure Network (PtCRIN) is the scientific partner of ECRIN in Portugal [31]. The scientific partners strive for developing and organize clinical research infrastructures, as well as to enable an increasing pattern of attractiveness and international competitiveness in innovation and quality. For that matter, ECRIN partners provide support to national investigators seeking to internationalize clinical trials (non-commercial trials) and involve their country in clinical trials initiated by investigators in other European countries.

1.3.5 Clinical Team

The clinical team represents a fundamental part of clinical studies. They are responsible for the conduct of the clinical trials at the health unit and coordination of the technical team involved. In medicine trials, the study team must be guided by a physician and the team is also composed of other medical doctors, nurses, pharmacists responsible for the circuit of experimental medication, as well as other collaborators responsible for laboratory and administrative activities at the units. The principal investigator of the clinical study has among other responsibilities to: carry out the clinical study in accordance with GCP; inform and clarify all the participants; obtain the informed consent from each participant; ensure confidentiality in the preparation, conduct, and conclusion of the study. In other types of interventions, the study team varies according to the type of study but ideally, although not mandatory, all the procedures should comply with the GCP.

1.3.6 Participants

The patients or participants in a clinical study are the core stakeholders for clinical investigation. In order to be part of a clinical study, participants must be engaged voluntarily

and sign the informed consent [10]. They are usually recruited from an ordinary pool of patients at a trial site, but sometimes by referral from other clinics or through local advertisements.

Most clinical trials include participants with a specific disease that is the target for the therapy. However, some clinical trials are conducted on healthy participants or healthy volunteers. Expenses of healthy volunteers are commonly assured by the sponsor because they receive no direct benefit and may have to take leave from their ordinary work during the trial.

1.4 Commercial versus Non-Commercial Clinical Trials

Clinical studies can be divided into commercial trials (sponsored by a commercial organization, usually a pharmaceutical company) and non-commercial trials also referred as academic or investigator-initiated clinical trials (IICTs) (generally supported by a non-profit organization). In the commercial trials, the clinical investigator only executes the industry-defined protocol. In non-commercial trials, the investigator or his / her academic institution is responsible for the design and execution of the trial. Both types of clinical trials comply with the same requirements: compliance with GCP, national legislation and European legislation [32].

The pharmaceutical industry has always been the lead promoter of clinical studies across the world as they lead the technological advances, have the sources to conduct multinational clinical trials and are increasingly using global networks [9], [33]. The data gathered in these multinational trials is extremely important once it is needed global validation of a treatment efficacy in a broadest population, to find local answers where universal ones may not be valid and to continue improving health systems in emerging economies [9]. Besides that, the vast capacity to support and conduct the studies, as well as the high success rates of drug discovery, must be acknowledged.

However, there is an emergent concern. The main focus of the industry is on the company's molecule which is panted. This means that the primary interest of commercial sponsors is on the commercialization of a product. Analysts have shown that innovative medical products appear on the market all too rarely and many drugs are just copies or analogues of products already on the market [34]. On top of that, rare diseases are an example of how the pharmaceutical research is dictated by profit. These are diseases difficult to study and mainly considered uneconomic- ie, too costly for a tiny market- so the pharmaceutical industry is not interested in rare diseases [33]. Nonetheless, these are trials of great economic interest to the

country as they represent a source of funding for the healthcare system. Typically, the main criteria of a pharmaceutical company to select the countries in which plans to conduct its trials are the potential of patients likely to enter the trial and the speed of approval. The selection of centers takes into account, among others, the reliability of recruitment, the identification of recognized investigators in their field and the experience in previous clinical trials [32].

On the other hand, throughout the last decade, the number of non-commercial trials has stagnated in most European countries, mainly those involving the use of medicines. This is due to the increased burden of laws, regulations, and costs that turns conducting clinical trials complex, time-consuming and expensive [35]. Indeed, the issues raised by a 2014 series from The Lancet on "Increasing value, reducing waste in biomedical research" persist [36]. A study carried out by PtCRIN, shows that for all registered trials from inception to July 2015, the average number of IICTs per total number of registered clinical trials in Europe is 17% [31]. Despite the few IICTs, the information provided in these studies is vastly important once they are instigated by academic researchers and generally focuses on questions not relevant to the industry. These clinical trials do not aim at the protection of commercial interests, being important for the wellbeing of the society. Typical examples are therapeutics optimization, comparison of treatments, "proof-of-concept" studies, orphan disease studies, pediatric trials, etc [33], [37]. Above all, these trials provide the robust evidence to enable policymakers to make informed and sustainable policy decisions on public health; lead to scientific communications and publications in scientific journals with higher IF (Impact Factor); help building scientific teams, which are the basis for center to be considered as reference.

1.5 Clinical Trials Registries

Clinical trials registries are public websites where the protocols and results information of clinical studies are registered. The registration of every trial in a registry is currently, and since 2007, a prerequisite for publication as established by the International Committee of Medical Journal Editors (ICMJE) and the FDA [38], [39]. This prerequisite is moving towards transparency in clinical research where the data gathered in every trial must be shared to avoid selective publication and selective reporting of research outcomes and to prevent unnecessary duplication of research effort [40]. Failure of transparency conflicts with the bedrock ethical principles governing clinical research (justice, beneficence, and respect for subjects) and the good publication practice guidelines [41].

There is an online database that contains the trial registration datasets provided by 14 clinical trials registries, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) [42]. For this investigational project, we just focused on four of the clinical databases: EU-CTR (EU Clinical Trials Register), Clinicaltrials.gov, ISRCTN (International Standard Randomised Controlled Trial Number Register) and ANZCTR (Australian New Zealand Clinical Trials Registry).

EU-CTR is the European database and only contains information about interventional studies on medicines conducted in the EU, or the European Economic Area (EEA) which started after 1 May 2004. This is the database used by national medicines regulators for data related to clinical trial protocols. The data on the results of these trials are entered into the EudraCT registry by the sponsors themselves and are published in this Database once the competent authorities have validated the data. The current number of clinical studies registered on this website is 35 340, of which 5 785 are trials conducted with subjects less than 18 years old (assessed in 20/07/2019).

Clinicaltrials.gov is a service of the United States National Institutes of Health (US-NIH) and includes all types of studies (interventional and observational) conducted in the world. Most of the records on ClinicalTrials.gov describe interventional clinical. As observational and interventional studies without medicines are not required by law to be registered this database does not contain information on all clinical studies. The database was launched in 2000 and the studies listed are conducted in all 50 States and in 209 countries. The current number of clinical studies registered on this website is 311 536 (assessed in 20/07/2019) being the largest clinical trial registry besides WHO ICTRP.

ISRCTN - International Standard Randomised Controlled Trials Number - is a registry database launched in 2000. The clinical studies included are both observational and interventional trials performed not only in the United Kingdom. The current number of clinical studies registered on this website is 18 379 (assessed in 20/07/2019).

ANZCTN - Australian New Zealand Clinical Trials Registry - is an online register of clinical trials being undertaken in Australia, New Zealand and elsewhere. It includes only interventional trials and it was launched in 2005. In 2007 was recognized by WHO ICTRP as one of the first Primary Registry. The current number of clinical studies registered on this website is 25 310 (assessed in 20/07/2019).

All the databases described above were created to register the protocols and results of clinical studies conducted worldwide and to turn this information publicly available. Despite that, all of the registries are different which makes it challenging to analyze them. In fact, a clinical study can be registered in more than one database and sometimes the information given in those databases is not consistent.

In a recent study upon the identification of sources of funding for non-commercial trials in Portugal, it was possible to report on the quality of information collected from clinical trial databases [28]. This study revealed that of the 282 Non-Commercial trials in Portugal, 235 are registered in just one database while 47 are registered in two or three clinical trial registries. Of the 47 clinical registries, only 13 studies had consistent information in all databases while 34 had inconsistent information. Regarding the "Non-Commercial Status" of the trial, only EU-CTR provides clear information while Clinicaltrials.gov and ANZCTR have clear information but it is not always provided and ISRCTN does not have this information. In terms of "Funding Source" and "Secondary ID" all clinical trial databases have clear information but it is not always provided. This study clearly reveals the urgent need to improve the databases for consistent registration and easiest elucidation of clinical studies.

1.6 Publication of Clinical Trials Results

In addition to the registration and publishing of results in clinical trial databases, ICMJE proposes responsible data sharing in scientific articles [40]. Even though posting clinical trial data on public databases may facilitate the good publication practice, publication of the results in medical journals has the potential to reach additional and varied stakeholders, providing a valuable contribution to data disclosure. Dikran Toroser *et al.* state that failure to publish clinical trial results can lead to dissemination bias and incomplete reporting, which may have a number of consequences, such as poor understanding of the scientific state of the art, inefficient allocation of resources for health interventions, potential inhibition of regulatory and public health decision making, and potential exposure of future clinical trial patients to unnecessary risk [43].

Although publishing of results in scientific literature is hardly recommended, many clinical trials do not have their results published and publication is conditioned. When the new European regulation in clinical research, comes into force, the publication of trials results (positive and negative) will become mandatory [44]. In fact, prior studies have sought to

determine the factors influencing the publication of clinical studies results. Publication bias that results in the preferential reporting of trials with positive outcomes is well-documented; trial discontinuation and industry funding have been reported as detrimental to publication, whereas larger studies and statistically significant results make publication more likely [45].

The information given upon a clinical trial should be exactly the same in the online database and correspondent scientific article, but studies have found inconsistencies [28]. Within 77 published studies, and regarding the funding source, 30 were consistent with the registry while 14 were inconsistent and 16 had additional information to the registry [28]. This evidences the necessity to full disclosure of information concerning clinical studies.

1.7 Publications Indicators

The quality of a scientific contribution is primarily estimated from the long-term impact that it has in science and the Journal Quality Indicators are important to reflect the impact and relevance of a publication. Some of the methodologies used to assess journal quality include citation analysis, journal's impact factor and percentile. For this research project, the website used for this analysis was Web of Science.

The journal impact factor (IF) or journal impact factor (JIF), first conceived in 1955 by Eugene Garfield, the founder of the Institute for Scientific Information (ISI), has been extensively used in the past decades as an index of quality of scientific journals and is based on citation analysis [46]. It is a measure reflecting the yearly average number of citations to recent articles published in that journal. It is calculated by dividing the number of citations in the current year to articles published in the two previous years by the total number of articles published in the two previous years as shown below.

$$\mathbf{IF}_y = \frac{\mathbf{Citations}_{y-1} + \mathbf{Citations}_{y-2}}{\mathbf{Publications}_{y-1} + \mathbf{Publications}_{y-2}}$$

A JIF of 1.0 means that, on average, the articles published one or two years ago have been cited one time. A JIF of 2.5 means that, on average, the articles published one or two years ago have been cited two and a half times. Therefore, journals with higher impact factors are often deemed to be more important than those with lower ones.

The usage of JIF as a measure of journal quality has been criticized once some authors state that it is a visibility measure rather than a quality one. This measurement depends heavily on the research field and the two-year period of time is a narrow window once the time between submitting and publishing a paper is considerable. Nevertheless, IF are useful in establishing the influence journals have within the literature of a discipline and must be used with an understanding of the limitations [47].

Based on Impact Factor (IF) data, the Journal Citation Reports published by Thomson Reuters provides yearly rankings of science and social science journals, in the subject categories relevant for the journal (in fact, there may be more than one).

The JIF Percentile is one of the measurements as it transforms the rank in category by JIF into a percentile value, allowing more meaningful cross-category comparison. It is calculated by using the following formula:

$$Journal\ Impact\ Factor\ Percentile = \frac{(N - R + 0.5)}{N}$$

N is the number of journals in the category

R is the Descending Rank

The Quartiles can be inferred from JIF Percentiles and are divided in four. Q1 denotes the top 25% of the IF distribution, Q2 for middle-high position (between top 50% and top 25%), Q3 middle-low position (top 75% to top 50%), and Q4 the lowest position (bottom 25% of the IF distribution). Given that, Q1 publications are considered more relevant that those with Q2, Q3 or Q4.

The total number of citations of a paper is the most basic citation metric. Once a paper is published it can later be cited in other papers. This quality measure is simply calculated as the number of times a paper, or a collection of papers has been cited over a particular time period. This measure is accurate and robust but not unbiased. It depends on the research field once some subjects have much greater citation density than others, and it depends on the quality of the citation itself - is it correct to account all citations from whatever source as equal? [48].

Concerning the impact of Commercial and Non-Commercial clinical trials, there are still some divergences. Commercial studies are frequently published in high-impact scientific journals, given the complexity and dimension of the study, which is mandatory to achieve a meaningful result. On the other hand, non-commercial trials, usually have their results published in peer-reviewed scientific papers with low impact factors or are presented at conferences. Besides that, academic investigators' careers depend on publication of research results while for-profit companies mainly aim for approval of new products and in some cases for future prescriptions. Therefore, and according to Kasenda *et al*., it is more likely to publish non-commercial trials results than commercial ones [49].

1.8 Clinical Trials Around the World

The actual landscape of Commercial and Non-Commercial clinical trials around the world is well defined. The number of clinical studies has considerably expanded worldwide in the last decades but the number of the latter has stagnated in most European countries [35]. This is an imminent issue once obtaining funding for non-commercial trials is challenging and the expenses for conducting clinical trials are high.

In a study performed in 2015, regarding the trials registered in the WHO ICTRP from 2006 to 2013, it was possible to notice that sponsorship has a major influence on the unequal mapping of clinical trials around the world. The portion of industry-sponsored trials was higher in high and upper-middle-income countries when compared to low-income countries. Besides that, single-country trials were mainly non-industry sponsored (76.3%). This result portrays the discrepancy in trials sponsored by the industry and by non-profit organizations as the need for multinational trials without commercial intention is real to globally validate treatment efficacy in the broadest population and to improve health systems worldwide [9].

1.9 Clinical Trials in Portugal

In Portugal, the number of clinical trials has been undergoing a great deal of variation. As a matter of fact, when we analyze the data provided by the Infarmed from 2006 to 2018, we can see that Portugal reached the lowest number of clinical trials in 2011 (87 authorized clinical trials) but from that year on the number of clinical trials has been increasing (Figure 3). This data includes all the clinical trials with medicines in all of the phases sponsored both by industry or non-profit organizations. When analyzing the number of trials regarding the phases of drug development, since 2006 it is consistent that phase III trials are the most prevalent (Figure 4).

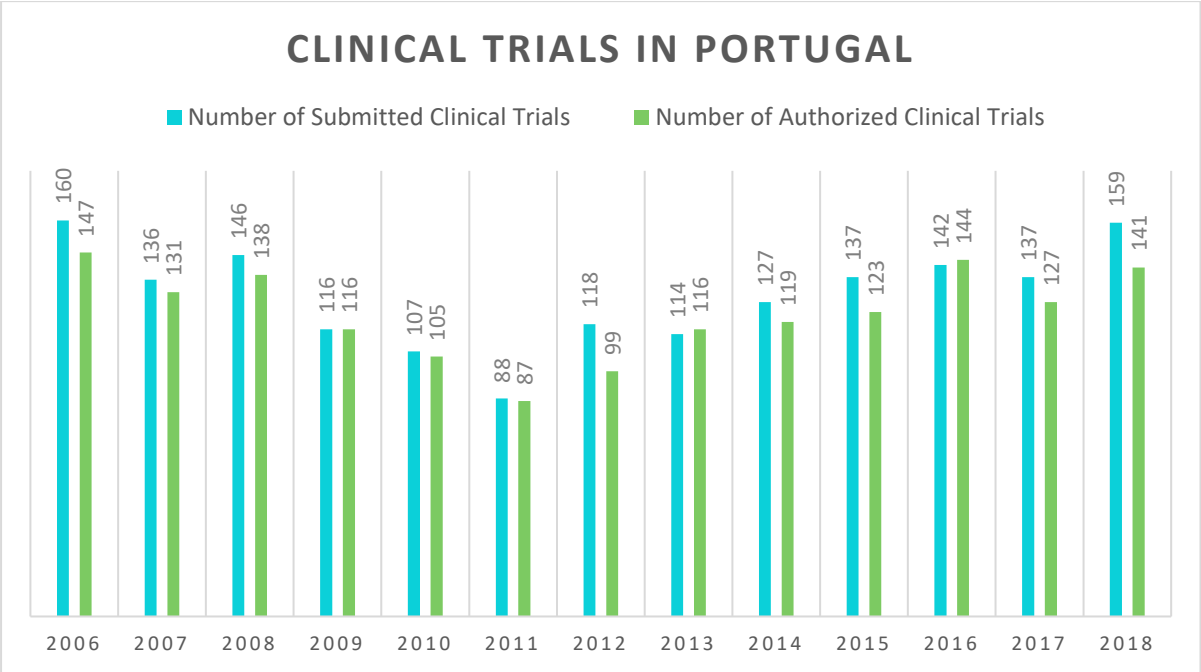

Figure 3: Clinical Trials in Portugal. Source: Infarmed.

Nonetheless, it is noteworthy to highlight that the number of Phase I trials has considerably increased throughout the years via bioequivalence clinical trials [32]. These results are important once we can apprehend that in Portugal most of the drugs being tested are in a late stage of the drug development process being the most expensive, time-consuming and difficult trials to design and run. Besides that, very few medicines are in the first stage of drug development implying that there are no new drugs being tested.

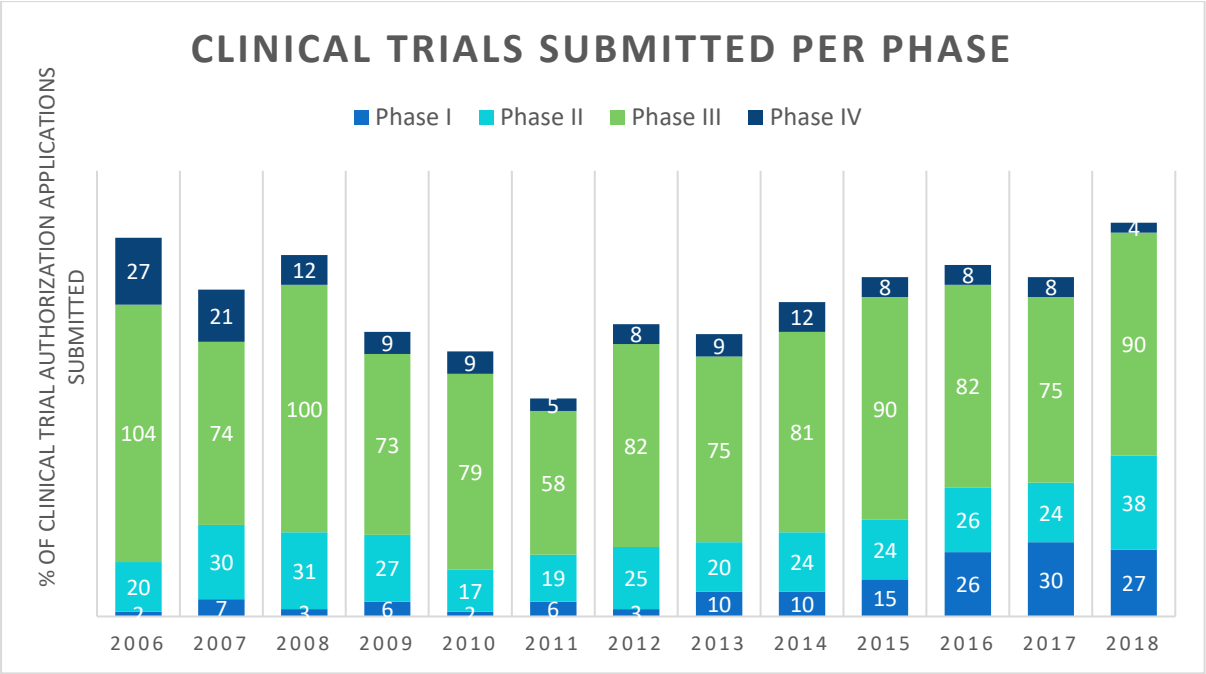

Figure 4:Evolution of the number of Clinical Trials submitted per phase. Source: Infarmed.

When we take into account the percentage of commercial and non-commercial clinical trials with medicines in Portugal, the latter are at a disadvantage (Figure 5). On one hand, Commercial Clinical trials have a great economic interest in the country, since they represent a source of funding for the health system. On the other hand, non-commercial trials are important because they capacitate clinical teams and lead to scientific communications and publications in scientific journals with higher IF that is essential for centers to be considered centers of reference. Since 2006 to date, Portugal presents a low percentage of non-commercial trials (from 3.6% to 14.0%). In other European countries, with similar size in population (Denmark, Belgium, Netherlands, and Sweden), this percentage varies between 18% and 45%, concluding that there is still room for growth for the investigator's initiative in Portugal [31], [32].

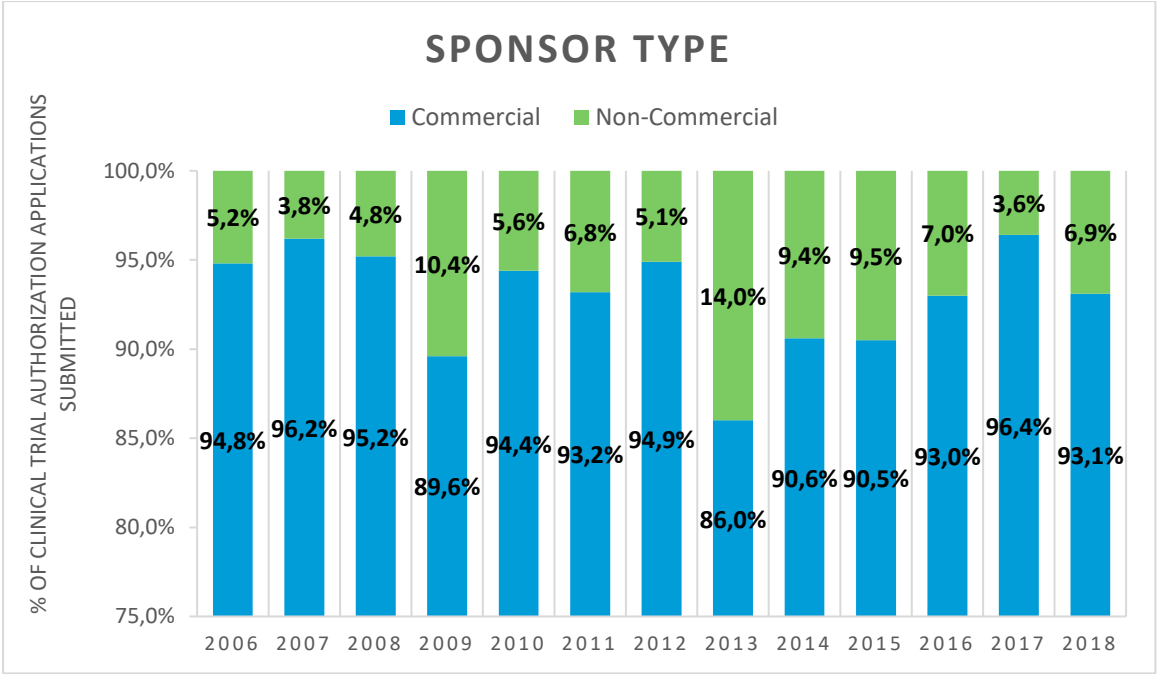

Figure 5: Evolution of the number of Clinical Trials by Sponsor. Source: Infarmed.

1.10 Relevance of the Work

The divergences between commercial and non-commercial clinical trials are important to be noticed in Portugal and there is an urgent need to understand and overcome this setback for the Portuguese institutions. Knowing the national outlook of clinical trials is the first step for achieving better results in our clinical investigation.

This research project provides an excellent opportunity to compare commercial and non-commercial trials using relevant variables that were not evaluated for Portugal so far. In fact, this is the first time in Portugal that 4 CTRs have been used to characterize all intervention studies and to crosscheck information with publications. In addition, the information gathered in this study was intended not only to achieve the primary objective related to the scientific impact of the publications but also to generate exhaustive data on the clinical trial tendencies performed in Portugal.

2. SCOPE AND AIMS

This research project was carried out under the framework of PtCRIN (Portuguese Clinical Research Infrastructure Network), based at Nova Medical School (NMS), which is the National Scientific Partner of ECRIN (European Clinical Research Infrastructure Network; www.ecrin.org). The aims of this research project are aligned with the work in progress in this infrastructure. During the last three years PtCRIN/NMS has been developing similar research projects, in collaboration with ECRIN, to increase the knowledge about current status of clinical trials involving Portugal as a recruiting country and/or sponsor, mainly focused on non-commercial trials.

The major goal of this research project was to assess the scientific impact of the publications from commercial and non-commercial clinical trials with Portuguese institutions as sponsor or/and with Portugal as participating country. Related to the primary goal, there were three secondary objectives intended to be assessed:

- The authorship of Portuguese investigators in publications derived from commercial and non-commercial clinical trials;
- The therapeutic areas and clinical study types with more scientific publications and registries;
- The median time from the end of a clinical trial to the publication of its results.

3. MATERIALS AND METHODS

In order to meet the primary goal of the research project, a systematic research in online clinical trial registries was made by two authors. The inclusion criteria of clinical trials registrations were: interventional trials starting from 01/10/2004 to 30/09/2018 with Portuguese Institutions as a sponsor or with Portugal as participating country. Four online clinical trial registries were used: Clincaltrials.gov, EUCTR, ISRCTN, and AZNCTR. All the trials meeting the criteria of inclusion were selected from each online registry and the information was extracted to an excel sheet to create the database for all the subsequent analysis.

3.1 Search Methodology of Trials in Each Database

Interventional clinical Trials registered and starting from 1st October 2004 to 30th September 2018 with Portugal as participating country or sponsor were identified by the methodology described step by step below and whose results are summarized in Figure 6. The first step was to search in each database for the trials, filtering the search using 3 filters: by Country – Portugal; by type of Study – Interventional; and by the period of time - from 01/10/2004 to 30/09/2018.

Step 1

In the Clinicaltrials.gov CTR, the three filters were applied as described above in an advanced search.

Step 2

The search in the EU-CTR allowed to include the timeframe from 01/10/2004 to 30/09/2018 and to select Portugal as country. As this CTR only includes interventional studies, the third filter was not needed.

Step 3

In the ISRCTN, it was not possible to refine the search besides selecting Portugal as the recruiting country and the period of time wanted. As so, the trials that were observational were immediately discarded.

Step 4

In the ANZCTR registry, an advanced search was performed using the three filters needed – country, type of study and period of time.

The following table describes the search methodology applied from step 1 to step 4 in all the clinical trials registries used (Table 2).

Table 2: Description of the search methodology used in each CTR and the code of the ID number of the trials.

	ClinicalTrials.gov	***EU-CTR***	***ISCTRN***	***ANZCTR***
Code	NCT	-	ISRCTN	ACTRN
Interventional	Study Type: Interventional Studies	Not Applicable	Not Possible	Study Type: Interventional
Country	Locations - Country	Select Country	Countries of recruitment	Countries of recruitment
Time frame	Additional Criteria: Study Start from - to	Select Date Range: from - to	Data applied: from - to	Trial start date: from – to
Link	www.clinicaltrials.gov	www.clinicaltrialsregister.eu	www.isrctn.com/	www.anzctr.org.au

EU-CTR: European Union Clinical Trials Register; **ISCTRN**: International Standard Randomised Controlled Trial Number Register; **ANZCTR**: Australian New Zealand Clinical Trials Registry

From the Step 1 to Step 4 some studies were automatically discarded, using as exclusion criteria based on: starting before 1/10/2004; non-interventional trials; sponsor or recruitment center not involving Portugal. The research results were reviewed individually by the author of this manuscript and other investigator (Daniela Matias) to confirm the compliance with the inclusion criteria.

3.2 Data extraction

For the extraction of each registration, we downloaded the information when possible (Clinicaltrials.gov; EU-CTR and ANZCTR) and extracted manually when not possible (ISRCTN). This information was gathered in one Excel sheet.

Step 5

Informative variables associated with the Identification (ID) Number of the trial, secondary ID, sponsor name, title of the study, start date and intervention type were firstly extracted. All trials identified were added to one excel sheet.

3.3 Identification of duplicates

Step 6

Following, a manual screening for duplicates was performed by the two authors, still independently from each other. This was important because the same trial may be registered in different databases without a reference to the secondary ID number. The screening was carried out through the trial ID, secondary ID, the title of the study and the Sponsor name. All the duplicates were gathered in the final sheet of Excel with the name "Duplicates phase 1" and were excluded from the analysis.

3.4 Division in Commercial and Non-Commercial Clinical Trials

Step 7

Both authors proceeded with a manual selection and division of the existing trials into Commercial and Non-Commercial ones. The selection was manual once the clinical trials registries do not have an unequivocal division of the trials in these two categories, with the exception of EU-CTR. This division is based on the sponsor type – for example if it is a pharmaceutical industry or a non-profit organization, respectively. At this phase, both authors had one only datasheet, in which the studies were categorized as "Commercial" and "Non-Commercial" trials.

3.5 Merging of authors Datasheets and Identification of trials to discard

Step 8-9

The excel sheets of the two authors were merged in one, retaining a total of 3551 clinical trials. Both authors agreed in a total of 1788 duplicates and discarded 11 trials: 9 trials from ISRCTN and 2 from EUCTR, which were observational trials (not in agreement with the inclusion criteria), reaching a total of 1752 trials for the analysis.

3.6 Division of Datasheets Regarding the Classification of Trials

Step 10

At this point, two datasheets were created as a result of the division of Commercial (n=1410) and Non-Commercial trials (n=342).

3.7 Identification of Trials to Discard

Step 11

A secondary search for discarded trials was performed and from the Commercial trials, a total of 8 trials were discarded (5 EUCTR and 3 ISRCTN trials were observational, 1 Clinicaltrial.gov trial did not have Portuguese Institutions as a sponsor or Portugal as a participating country, and 1 Clinicaltrial.gov trial was a duplicate). From the Non-Commercial trials a total of 3 trials were discarded (1 Clinicaltrials.gov trial was observational, 1 Clinicaltrial.gov trial did not have Portuguese Institutions as a sponsor or Portugal as a participating country, and 1 ANZCTR trial was duplicated). After all, the systematic and independent search made by the same two investigators, a total of 1402 Commercial and 339 Non-Commercial trials were included for the work of investigation.

3.8 Complementary Information

Finally, with all the trials for the analysis selected, the information needed to complete the database was searched using the clinical trials IDs in the correspondent online registries. The information collected was the Sponsor's Country, Status of the Trial, Completion Date, Therapeutic Area, Design of the Trial, Number of Patients, Phase of the trial, Number and name of Participating Countries, Participating sites and Funders. When not specified, the information was filled with "Not Identified".

All disagreements were solved by consensus by two different investigators (Catarina Madeira and Joana Batuca). From here on out, the search was performed by the author of the present work.

Step 12

The data concerning the General Status of the trial was deducted from the extracted data. The trials were considered "Completed" when the status of the trial was "completed" or "prematurely ended", "terminated" or "unknown" if the clinical trial registry provided the end competition date of the trial.

3.8 Identification of Published Trials

Step 13

In order to search for potential publications of the clinical trials, a search on PubMed was carried out. The clinical trials primary and secondary IDs of completed trials were used to perform this search.

Only completed trials concerning the results of the trial with the trial ID on the Abstract were considered and only one publication per trial was counted. Publications of the protocols, comparative studies, publications without the trial ID on the Abstract or publication prior to the completion date of the trial were excluded. For the completed trials with only one publication, the paper was considered if it was in accordance with the inclusion criteria. However, for the trials with two or more publications, the publication selected was the first publication with results starting from the completion date of the trial.

3.9 Publication's Complementary Information

Step 14

After the selection of all the publications, information about the Date of Publication, Portuguese Authorship, Participating Centers, Journal name, DOI (digital object identifier), trial's Funders was collected. When in disagreement with the information collected from the clinical trials database, the information provided in the publication was considered as the correct one.

Data concerning time spent from the end of the trial to the publication of the results was deducted as the difference between the publication date of the results and the completion date of the trial.

The information on the funders of the clinical trials was identified in different fields from each CTR. ISRCTN and ANZCTR are the only CTRs that have a specific field entitled "Funder". In EU-CTR the funder information was identified in the field "Sources of Monetary Support" and, in ClinicalTrials.gov, the funders were identified in the field "Sponsor and Collaborators". Once the information given upon the funder in ClinicalTrials.gov is not clear, when only the sponsor was mentioned in these CTR, it was considered as the funder and when there were more institutions besides the funder, only those institutions were considered as funding sources.

Taking into account the goal of the project, the publications IF and Quartile was sought. This information was searched on Web of Science. For the 2019 publications, these fields were completed with "Not Applicable" once the information is not yet available. Besides that, for the 2018 publications, the IFs and Quartiles used were the ones correspondent to 2017.

3.10 Variables assessed

The variables analyzed in this study are represented in Table 3.

Table 3: All variables used for analysis, correspondent classification and indication of where the information was obtained from.

VARIABLE	*TYPE OF VARIABLE*	*OBTAINED FROM CTR*	*OBTAINED FROM PUBLICATION*
Completion Date	Numeric Discrete	Yes	-
Date of Publication of Results	Numeric Discrete	-	Yes
Funder Type	Categorical Nominal	Yes	Yes
Funding Agency	Categorical Nominal	Yes	Yes
Impact Factor of the Journal	Numeric Continuous	-	Yes*
Intervention Applied	Categorical Nominal	Yes	-
Internationalization	Categorical Nominal	Yes	-
Portuguese Authorship	Categorical Nominal	-	Yes
Quartile of the Journal	Numeric Discrete	-	Yes*
Sponsor Name	Categorical Nominal	Yes	-
Sponsor Type	Categorical Nominal	Yes	-
Start Date	Numeric Discrete	Yes	-
Status of the Trial	Categorical Nominal	Yes	-
Therapeutic Area	Categorical Nominal	Yes	-
Time spent from end of trial to publication of results	Numeric Discrete	Yes	Yes
Trial Phase	Categorical Ordinal	Yes	-

*see section 3.9; **CTR**: Clinical Trials Registry

3.11 Categorization of the Variables

Funder Type

Funders were coded as being **(i)** a non-profit organization (eg, public institution, funding agency, disease-specific organizations), **(ii)** a for-profit organization (ie, private company/industry), **(iii)** both, when funding was provided by industry and non-profit organization(s), **(iv)** no funding when the authors declared that no funding was obtained for the trial and **(v)** not indicated, when the information was not provided.

Funding Agency

Funding agencies were only assessed for the non-commercial clinical trials and were coded as being **(i)** international, if the headquarters is not in Portugal **(ii)** national, if the headquarters is in Portugal **(iii)** both, when there were both national and international funding agencies **(iv)** not applicable when the trial did not have funding agencies support and **(v)** not indicated, when the information was not provided.

Intervention Applied

Interventions were coded as being **(i)** chemical drug, **(ii)** biological/biotechnological drug, **(iii)** behavioral interventions, **(iv)** device, **(v)** diagnostic, **(vi)** nutrition, **(vii)**, surgery **(viii)** procedure, **(ix)** radiation, **(x)** rehabilitation and **(xi)** other.

Internationalization

Trials were coded as being **(i)** national (only performed in Portugal) or **(ii)** multinational (performed in Portugal and other countries).

Sponsor Type

Sponsor type was coded as being **(i)** pharmaceutical industry, **(ii)** university, **(iii)** hospital, **(iv)** foundation, **(v)** disease-specific organization, **(vi)** research institute and **(vii)** other when the sponsor did not correspond to the previous classification (e.g. private clinics and governmental organizations).

Status of the Trial

Status of the trial was coded as being **(i)** completed, if the trial had an end date, was ended prematurely, stopped, terminated or withdrawn, **(ii)** ongoing, if the trial had no end date, was restarted or temporarily halted, and **(iii)** unknown if the CTR declared an unknown status.

Therapeutic Area

Therapeutic areas were coded as being **(i)** Ageing, **(ii)** Anesthesia, **(iii)** Cardiology/Vascular Diseases, **(iv)** Dental or Oral Health, **(v)** Dermatology, **(vi)** Endocrinology, **(vii)** Gastroenterology, **(viii)** Geriatric/Rehabilitation/Nursing Care/ General Practice, **(ix)** Hematology, **(x)** Infectious Diseases, **(xi)** Musculoskeletal/Rheumatology/Trauma, **(xii)** Nephrology, **(xiii)** Neurology, **(xiv)** Obstetrics/Gynecology, **(xv)** Occupational/Eating

habits/Sports/Sleep, **(xvi)** Oncology, **(xvii)** Ophthalmology, **(xviii)** Pediatrics/Neonatology, **(xix)** Psychiatry/Psychology, **(xx)** Pulmonary/Respiratory Diseases and **(xxi)** Urology.

Trial Phase

Trial phases for medicinal products development were coded as being **(i)** phase I, **(ii)** phase I/II, **(iii)** phase II, **(iv)** phase II/III, **(v)** phase III, **(vi)** phase III/IV, **(vii)** phase IV, **(viii)** not applicated if the trial did not concern medicinal products and **(ix)** not indicated if the information on the CTR was not clear.

3.12 Statistical Analysis

The analysis performed were descriptive statistical analysis performed using Excel controls. The presented values represent sums, percentage, and means and relative and absolute frequencies were calculated.

For the statistical analysis, data results are presented as mean ± standard error and were analyzed with IBM Statistical Package of Social Science version 25.0 (SPSS). Significance analyses were performed for p values < 0.05 using the Mann-Whitney-U test to evaluate the significance of the difference between two groups of independent samples. This non-parametric test was used in all cases because samples failed one of the t-test hypotheses: normal distribution or equality of variances confirmed using Shapiro-Wilk's and Levene's tests, respectively.

4. RESULTS

In order to achieve the main goal of this research project of assessing the scientific impact of the commercial and non-commercial clinical trials with Portuguese institutions as sponsor or/and with Portugal as participating country, a well-defined methodologic approach was required.

A total of 2672/2679 (Step 5, Figure 6) clinical trials were identified from the four CTRs, by each author. After the duplicates have been identified, 1763/1788 (Step 6, Figure 6) clinical trials were selected. Of those, after a second and third screening for duplicates and discarded trials, a total of 1741 clinical trials were identified and used for subsequent analysis (1402 commercial and 339 non-commercial) (Step11, Figure 6). Within the selected clinical trials, 970 commercial and 171 non-commercial trials were completed (Step 12, Figure 6). Of those, and considering all the inclusion criteria for publication screening, a total of 280 publications were found for commercial trials and 54 for the non-commercial ones (Step 12, Figure 6). Portuguese authors appear in 24 publications of the commercial clinical trials and in 38 publications of the non-commercial clinical trials (Step 14, Figure 6)

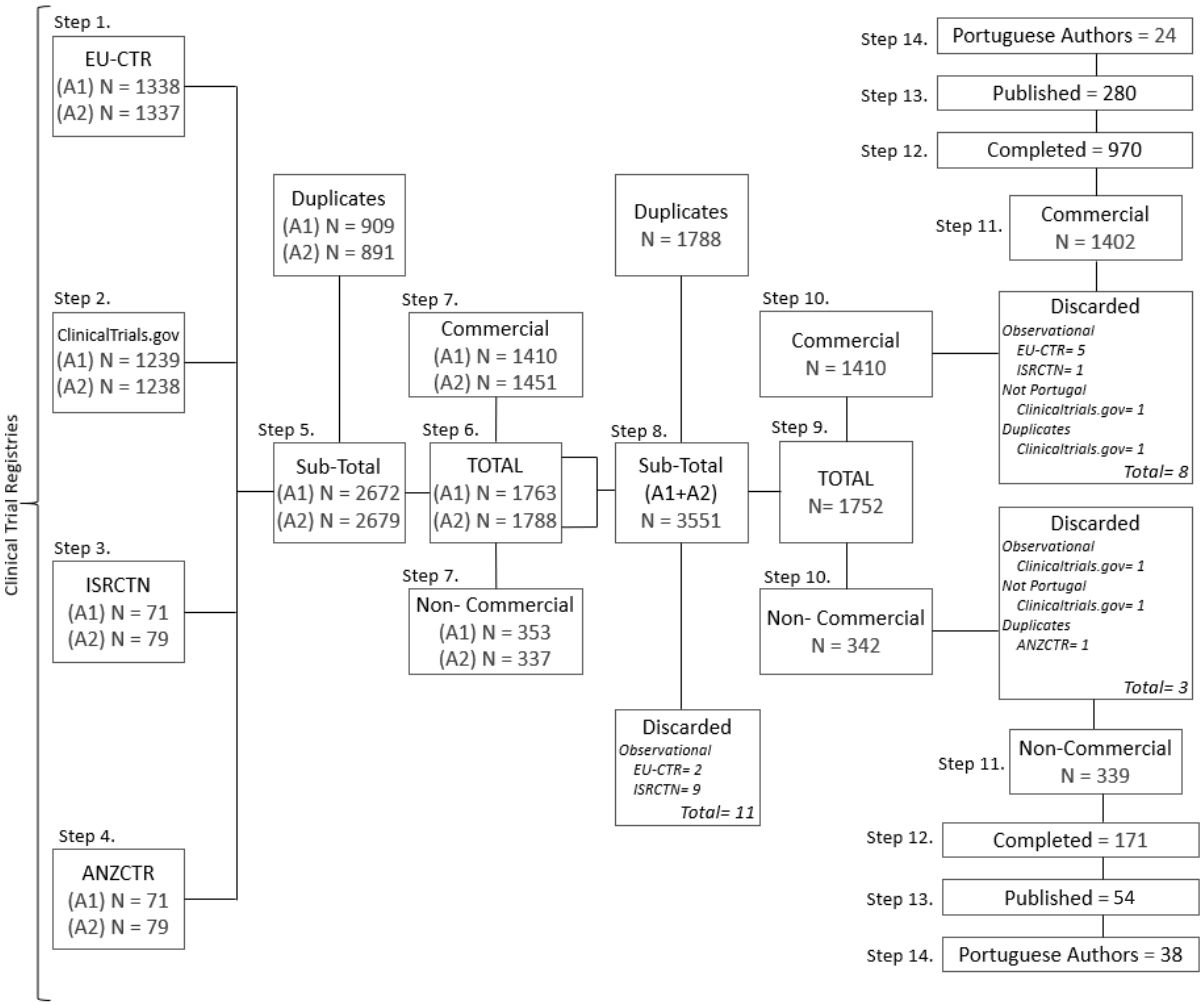

Figure 6: Flowchart representing the systematic search of the interventional commercial and non-commercial clinical trials, involving Portugal as a participating country or sponsor.
The search was performed in four clinical trial registries, CTRs (EU-CTR, Clinicaltrials.gov, ISRCTN, and ANZCTR). Studies starting from 01/10/2004 until 30/09/2018 were identified in each of the databases separately (Steps 1-4). After separating discarded and duplicated trials, all remaining studies were gathered in one Excel sheet (Step 5-6). A further classification in commercial and non-commercial clinical trials was performed (Step 7). The two authors' sheets were merged and after separating discarded trials the sheets were divided into two: commercial and non-commercial clinical trials (Step 8-10). Duplicate studies were also discarded, and the final number of trials was cleaned and harmonized (Step 11). Further details were collected from all the databases, including the identification of completed studies (Step 12). Publications published until December 2017, with results from completed studies were identified (Step 13-14).

Although the key target of the research is based on clinical trials that are published, these results are only more relevant and meaningful if an analysis of the baseline data is performed. The baseline data refers to the total of 1741 interventional clinical studies, whether they are published or not. Hence, the first approach included all the clinical trials that were in accordance with the inclusion criteria – 1402 commercial clinical trials plus 339 non-commercial clinical trials (Figure 6). It is important to acknowledge which type of clinical trials are in the ground

of the analysis to understand the characteristics of the clinical trials that achieve the publication of the results.

4.1 Commercial Clinical Trials

Taking into account all the search methodology for the screening of the clinical trials to include in this research project, a total of 1402 commercial clinical trials were included for analysis. These are interventional clinical trials, starting from 01/10/2004 to 30/09/2018 with Portuguese institutions as sponsor or with Portugal as participating country and were found in the four registries used.

4.1.1 Status of the Clinical Trials and correspondent Therapeutic Areas

The first step for the analysis included a generical overview of the commercial clinical trials. Therefore, the overall number of clinical trials was considered as well as the status and therapeutic areas studied.

The number of commercial clinical trials with Portugal as a participating country or sponsor has evolved throughout the years and the value oscillated from 106 to 220 trials per pair of year considering the years from 2005-2006 to 2017-2018 (see Appendix A 1).

Considering the status of the commercial clinical trials, the majority of them are completed (n= 970; 69.19%) and 419 (29.89%) of them are still ongoing (Table 4). A residual percentage of the clinical trials were not authorized (n= 9; 0.64%), classified as unknown (n= 3; 0.21%) or the status was not identified (n= 1; 0.07%) (Table 4). From the 419 commercial trials that are still ongoing, most of them are studies in the therapeutic area of oncology (n= 158; 37.71%) and initiated in 2017 or 2018 (n= 152; 36.28%) (see Appendix A 2 and A 3).

Table 4: Status of the commercial clinical trials. Results are represented as the total number (N) and as percentage of trials (%).

STATUS	***Number of Clinical Trials (N)***	***Percentage of Clinical Trials (%)***
Completed	**970**	**69.19**
Ongoing	**419**	**29.89**
Not Authorized	**9**	**0.64**
Unknown	**3**	**0.21**
Not Identified	**1**	**0.07**
TOTAL	**1402**	**100.00**

Relatively to the therapeutic areas studied in all the commercial clinical trials considered for analysis, there are five highlighted areas: Oncology (n= 351; 25.04%) in first, followed by Neurology (n= 148; 10.56%), Cardiology/Vascular Diseases (n= 135; 9.63%), Infectious Diseases (n= 123; 8.77%) and Musculoskeletal/Rheumatology/Trauma (n= 111; 7.92%) (Figure 7). Commercial studies with other therapeutic areas can be found in Appendix A 4.

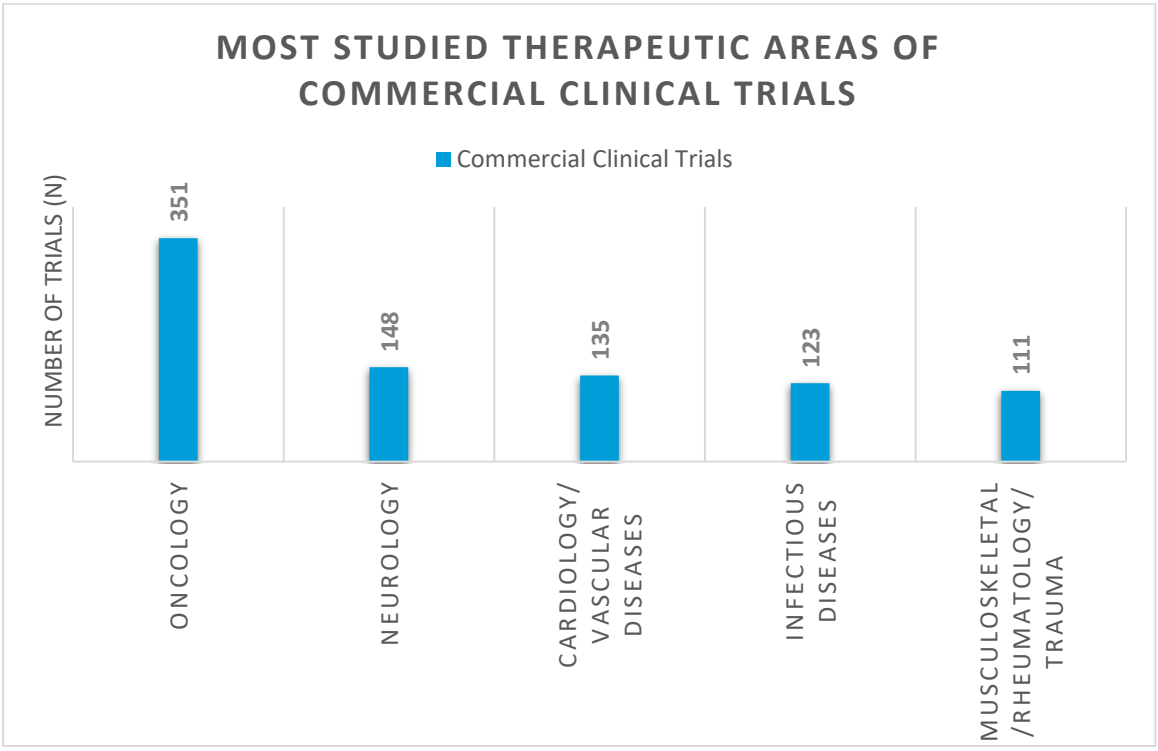

Figure 7: The five most studied therapeutic areas of commercial clinical trials represented by the total number of clinical trials (N= 1402).

4.1.2 Interventions applied in the Commercial Clinical Trials

The majority of commercial clinical trials had chemical drugs as intervention (n= 880; 62.77%) followed by biological/biotechnological drugs (n= 465; 33.17%) (Figure 8A). Only 3.71% (n= 52) of the trials used medical devices and a residual percentage of 0.35% (n= 5) applied procedures, radiation or other types of interventions. Medicinal products (chemical drugs or biological ones; n= 1345) are the most common interventions used in the clinical practice and are guided by four phases of drug development. Phase III trials are the most common and are studied in 928 commercial clinical trials in Portugal (Figure 8B).

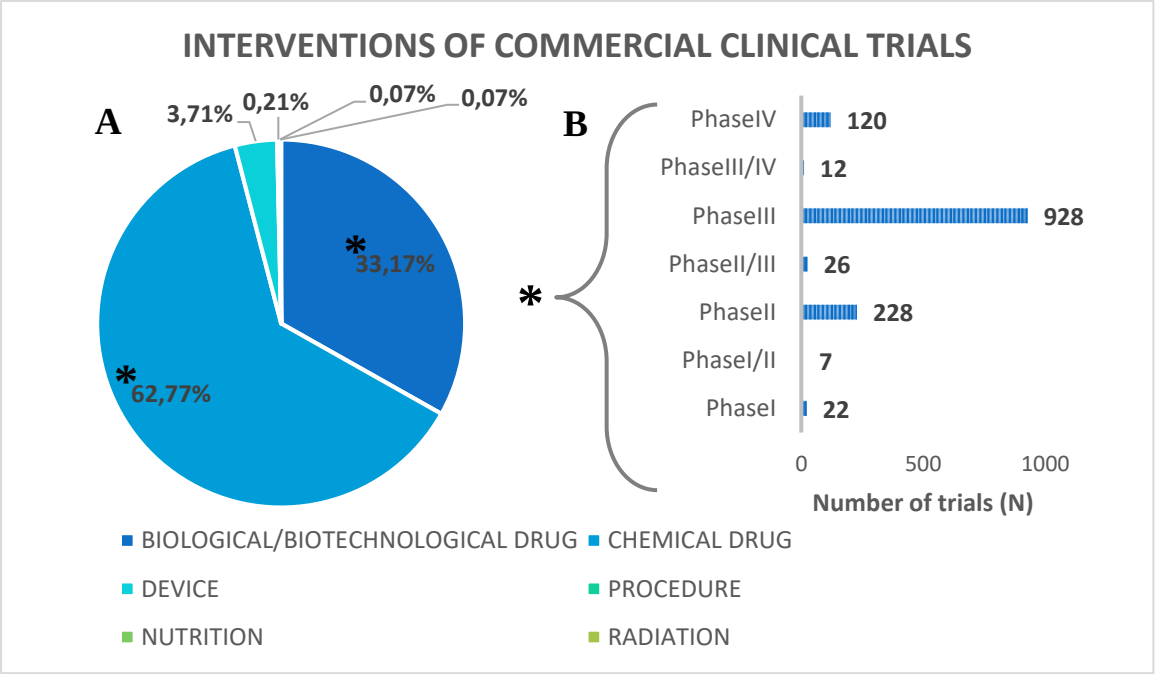

Figure 8: Types of interventions applied in the commercial clinical trials and phases for the trials for medicinal products.
(A) Percentage of the type interventions applied categorized by Biological/Biotechnological Drugs; Chemical Drugs; Devices; Procedures; Nutrition, Radiation. (B) The number of trials divided into trial phases for the medicinal products (both chemical and biological/biotechnological drugs, N=1345, 2 trials did not mention the phase).

4.1.3 Companies Sponsoring Commercial Clinical Trials

Taking into account that all the commercial clinical trials included are sponsored by the pharmaceutical industry, an analysis of which countries and which pharmaceutical companies are sponsoring the clinical trials was performed. Analyzing the top six countries sponsoring commercial clinical trials, USA is the leading one, sponsoring a total of 419 trials (29.89% of

all commercial trials). Following them, Switzerland sponsors 231 trials (16.48%) and Germany 159 (11.34%) (

Figure 9). Portugal appears in the list of the countries sponsoring the highest number of commercial clinical trials included in this research project, promoting 111 clinical trials (7.92% of all commercial clinical trials).

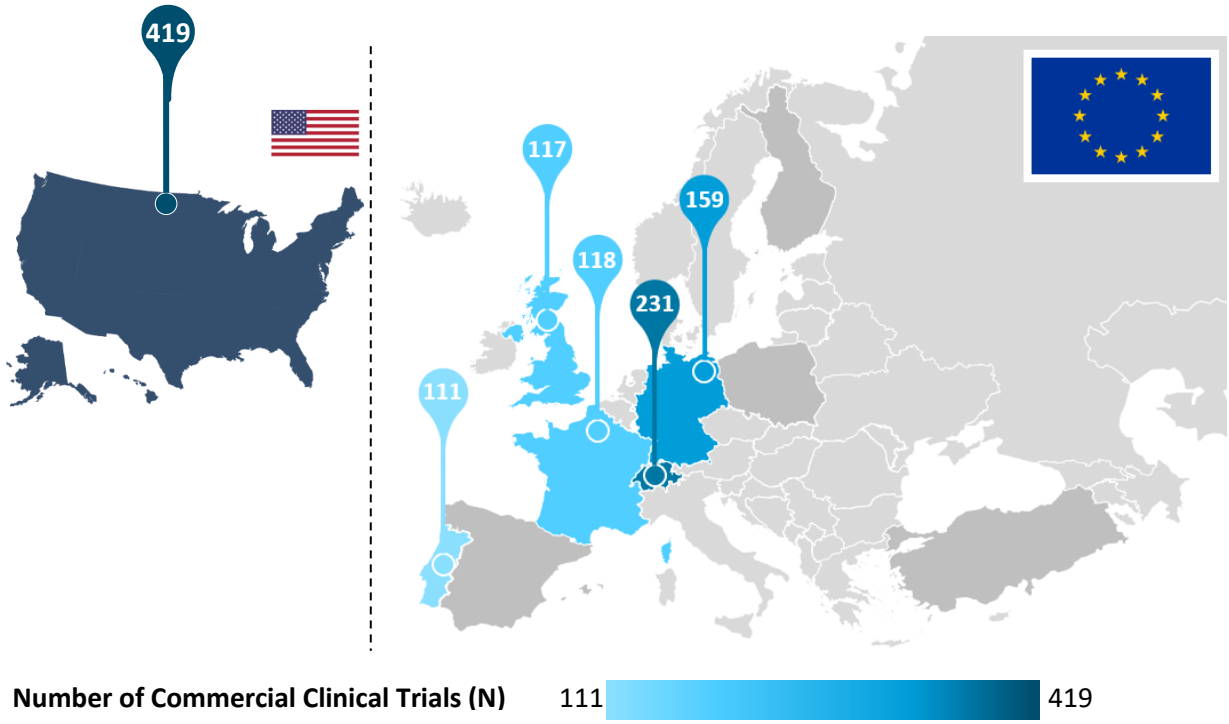

Figure 9: Representation of the Countries Sponsoring the highest number of Commercial Clinical Trials in Portugal.
Right Side represents Europe and Left side Represents the USA. Number of trials according to the country go from 419 trials in the USA; 231 in Switzerland; 159 in Germany; 118 in France; 117 in the United Kingdom (UK) and 111 in Portugal.

Within all the commercial clinical studies, the leading companies are Novartis, promoting 95 clinical trials; F. Hoffman-La Roche, promoting 94 clinical trials; Merck & Co., promoting 69 clinical trials; Pfizer and Sanofi, promoting 63 and 61 clinical trials, respectively (Figure 10). These are all multinational companies with high profits and headquartered in the United States of America (USA), Germany, Sweden, and France.

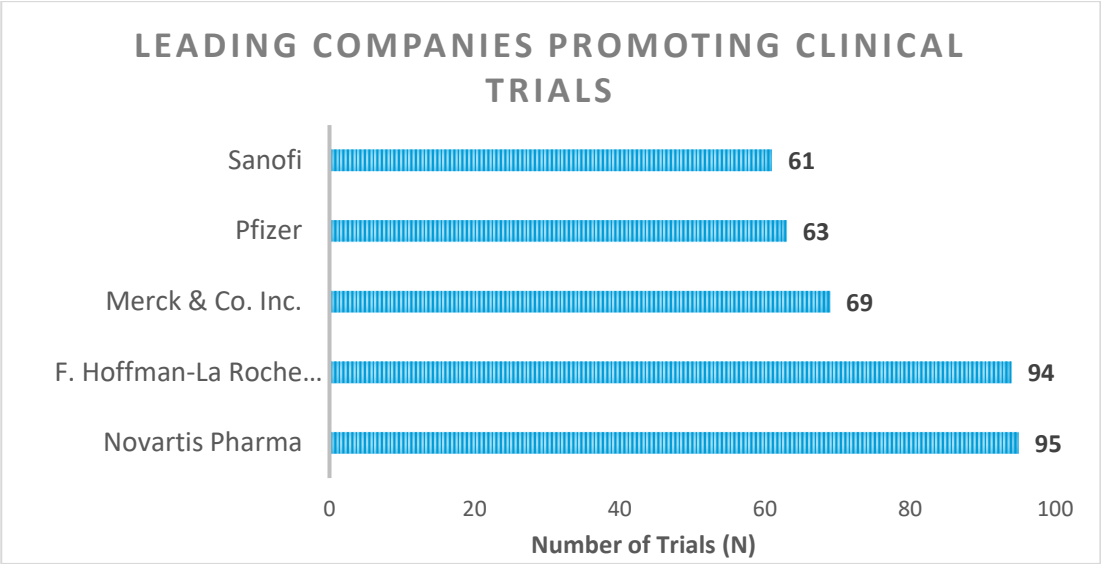

Figure 10: The number of commercial clinical trials categorized by the top five pharmaceutical companies as sponsors.

4.2 Non-Commercial Clinical Trials

Considering the search methodology for the screening of the clinical trials to include in this research project, a total of 339 non-commercial clinical trials were included for subsequent analysis. These are interventional clinical trials, starting from 01/10/2004 to 30/09/2018 with Portuguese institutions as sponsor or with Portugal as participating country and were found in the four registries used.

4.2.1 Status of the Clinical Trials and Correspondent Therapeutic Areas

The first step for the analysis included a generical overview of the non-commercial clinical trials. Therefore, the overall number of clinical trials was considered as well as the status and therapeutic areas studied.

Taking into account the evolution throughout the years, from 2005 to 2017, the number of non-commercial clinical trials performed with Portugal as a sponsor or participating county has increased. The curve has assorted from 21 to 84 clinical trials per pair of year and the maximum was reached in 2015-2016 (see Appendix A 1).

The status of the non-commercial clinical trials included in this research project can be divided in completed (n= 170; 50.15%); ongoing (n= 160; 47.20%) or unknown (n= 9; 2.65%) (Table 5). Only a residual amount of clinical trials does not have the status updated in the correspondent clinical trial registry. The 160 ongoing non-commercial clinical trials are mostly

in the therapeutic areas of Oncology (n= 55; 34.38%), starting in 2017 or 2018 (n= 54; 33.75%) (see Appendix A 2 and A 3).

Table 5: Status of the non-commercial clinical trials. Results are represented as the total number (N) and as percentage of trials (%) and divided as Completed; Ongoing or Unknown status.

STATUS	***Number of Clinical Trials (N)***	***Percentage of Clinical Trials (%)***
Completed	**170**	**50.15**
Ongoing	**160**	**47.20**
Unknown	**9**	**2.65**
TOTAL	**339**	**100.00**

According to the data results, non-commercial clinical trials are mostly studies concerning the following therapeutic areas: Oncology (n= 78; 23.01%), Cardiology/Vascular Diseases (n=44; 12.98%), Musculoskeletal/Rheumatology/Trauma (n=31; 9.14%), and Pediatrics/Neonatology (n= 20; 5.90%), (Figure 11). Geriatric/Rehabilitation/Nursing Care/ General Practice, Dental or Oral Health and Neurology follow this hierarchy and share the fifth place of the most studied therapeutic areas (n= 18; 5.31%). Contrarily, Dermatology is one of the therapeutic areas with a fewer number of non-commercial clinical trials (n= 2; 0.59%) (see Appendix A 5).

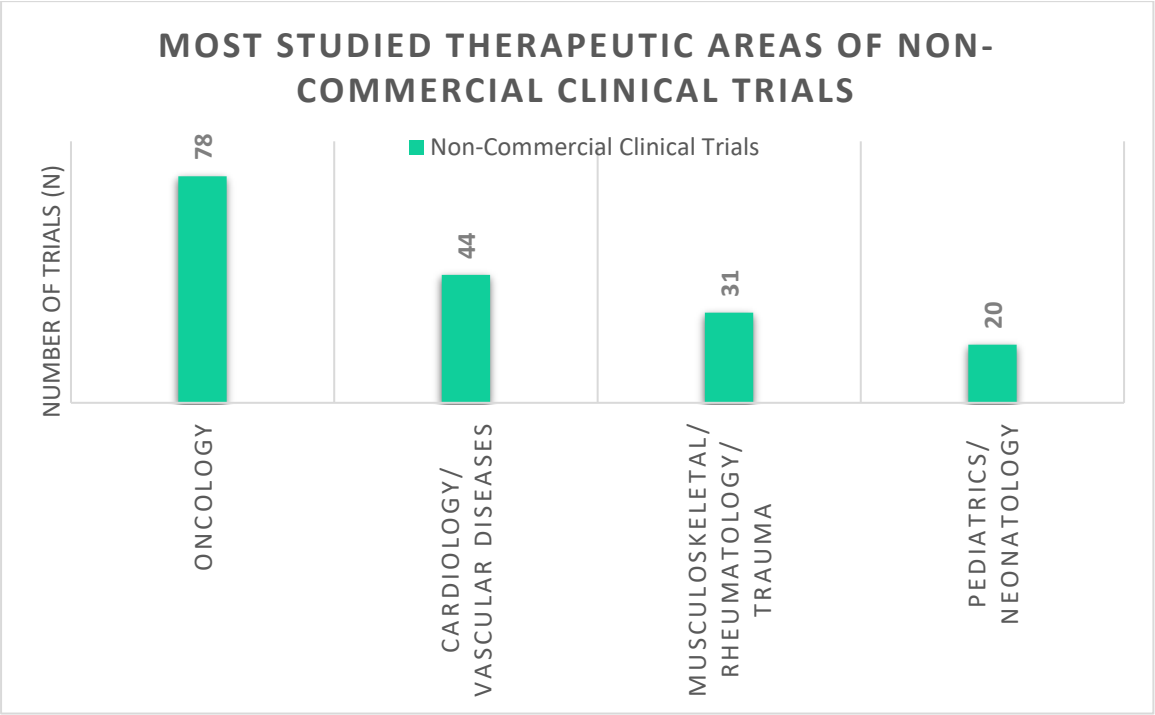

Figure 11: The four most studied therapeutic areas of non-commercial clinical trials represented by the total number of clinical trials (N= 339).

4.2.2 Interventions applied in the Non-Commercial Clinical Trials

The interventions applied in the non-commercial clinical trials can be diverse. The most used interventions were chemical drugs (n= 99; 29.20%) and behavioral interventions (n= 91; 26.84%) (Figure 12). Considering the clinical trials with chemical drugs or biological/biotechnological drugs (n= 99 + 42 = 141), the most studied phases of drug development are phase III trials (n= 55; 39.01%) (see Appendix A 6).

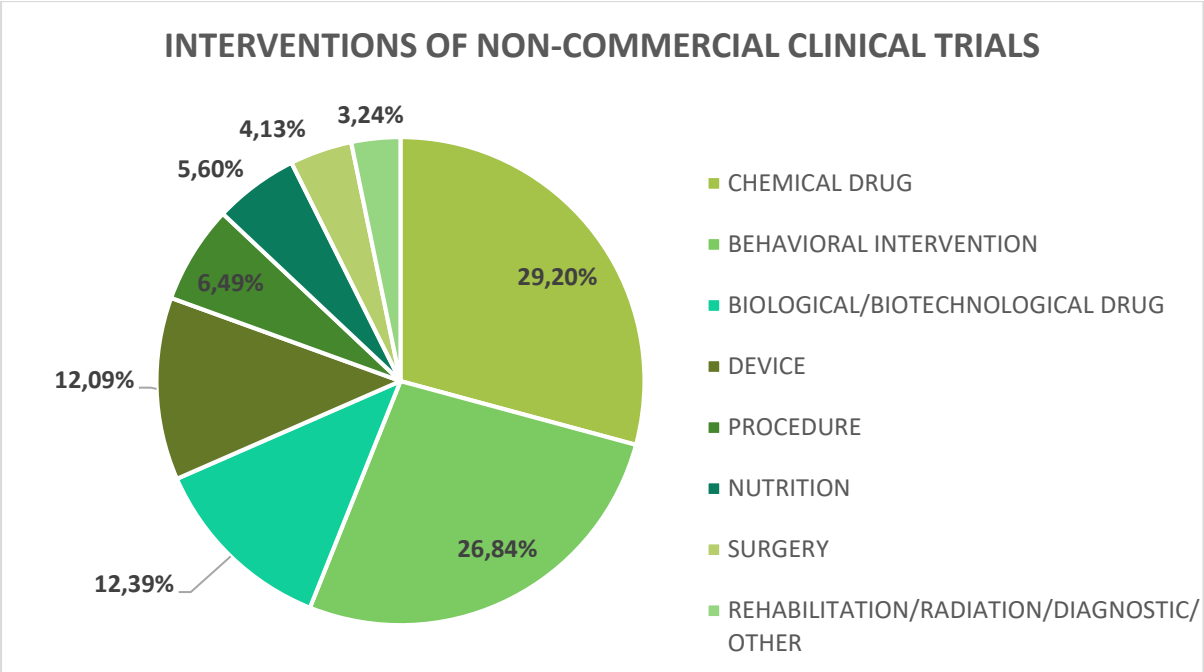

Figure 12: Percentage of the interventions applied in the non-commercial clinical trials (N= 339).

4.2.3 Type of Sponsor in the Non-Commercial Clinical Trials

Considering that the non-commercial clinical trials are generally supported by non-profit organizations and instigated by investigators, an analysis of which countries and which non-profit organizations are sponsoring the clinical trials was performed.

Analyzing the top six countries sponsoring non-commercial clinical trials, Portugal is the leading one, sponsoring a total of 215 trials (63.42% of all non-commercial trials). Following, the UK sponsors 20 trials (5.90%) and France 18 (5.31%) (Figure 13). After them, Germany follows with a percentage of 5.01% (17 trials), Spain with a percentage of 3.83% (13 trials) and Italy sponsors 12 trials (3.54%) (Figure 13).

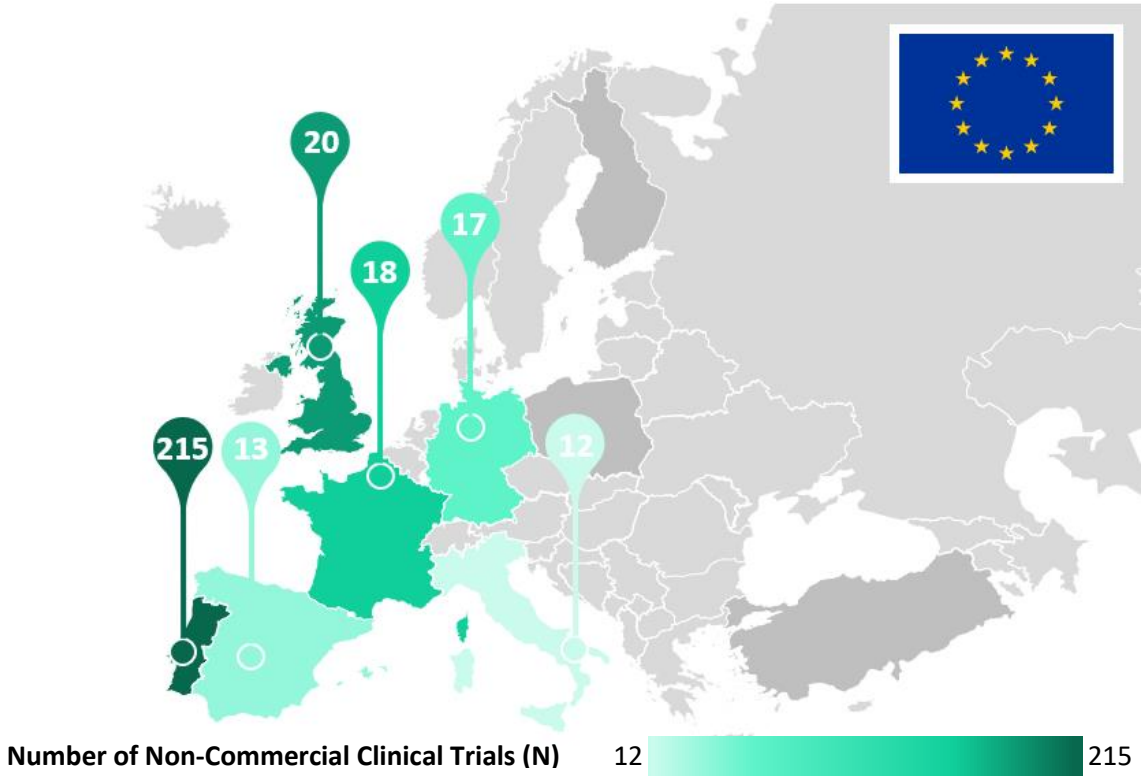

Figure 13: Representation of the Countries Sponsoring the highest number of Non-Commercial Clinical Trials in Portugal.
Number of trials according to country go from 215 trials in Portugal; 20 in the UK; 18 in France; 17 in Germany; 12 in Spain and 12 in Italy.

From the 339 non-commercial clinical trials, 154 are sponsored by a university (45.43%), 83 by a hospital (24.48%), 61 by a disease-specific organization (17.99%), 16 by a research institute (4.72%), 15 by a foundation (4.42%) and 10 by other types of non-profit organizations (2.95%) (Figure 14). The universities that sponsor more clinical trials are the University of Lisbon (n= 28; 18.18%) and the University of Porto (n= 28; 18.18%) (see Appendix A 7).

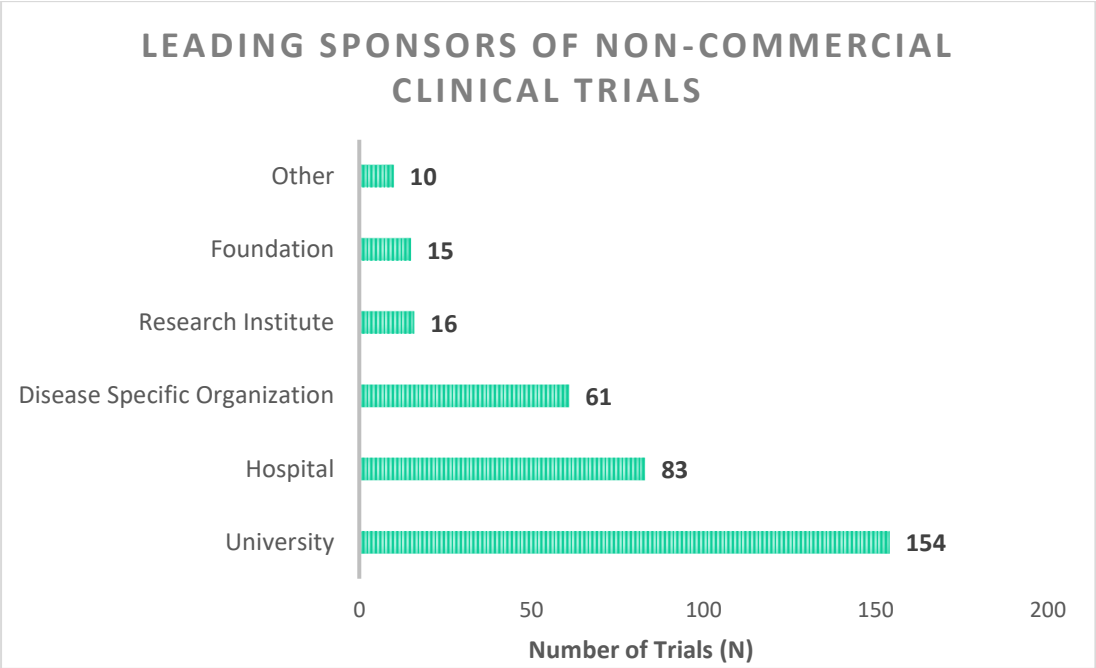

Figure 14: Number of clinical trials divided by type of sponsor for non-commercial clinical trials. Sponsors are divided as being: Universities; Hospitals; Disease-Specific Organizations; Research Institutes; Foundations; Other types of Sponsors like clinics and government organizations.

When crossing the sponsor type information with the internationalization of the trial, we can see a trend in the results (Figure 15) where foundations, disease-specific organizations, and research institutes are the sponsors of higher number of multinational clinical trials when compared to universities and hospitals. The latter and other sponsor types, such as clinics and government organizations, mostly sponsor national trials.

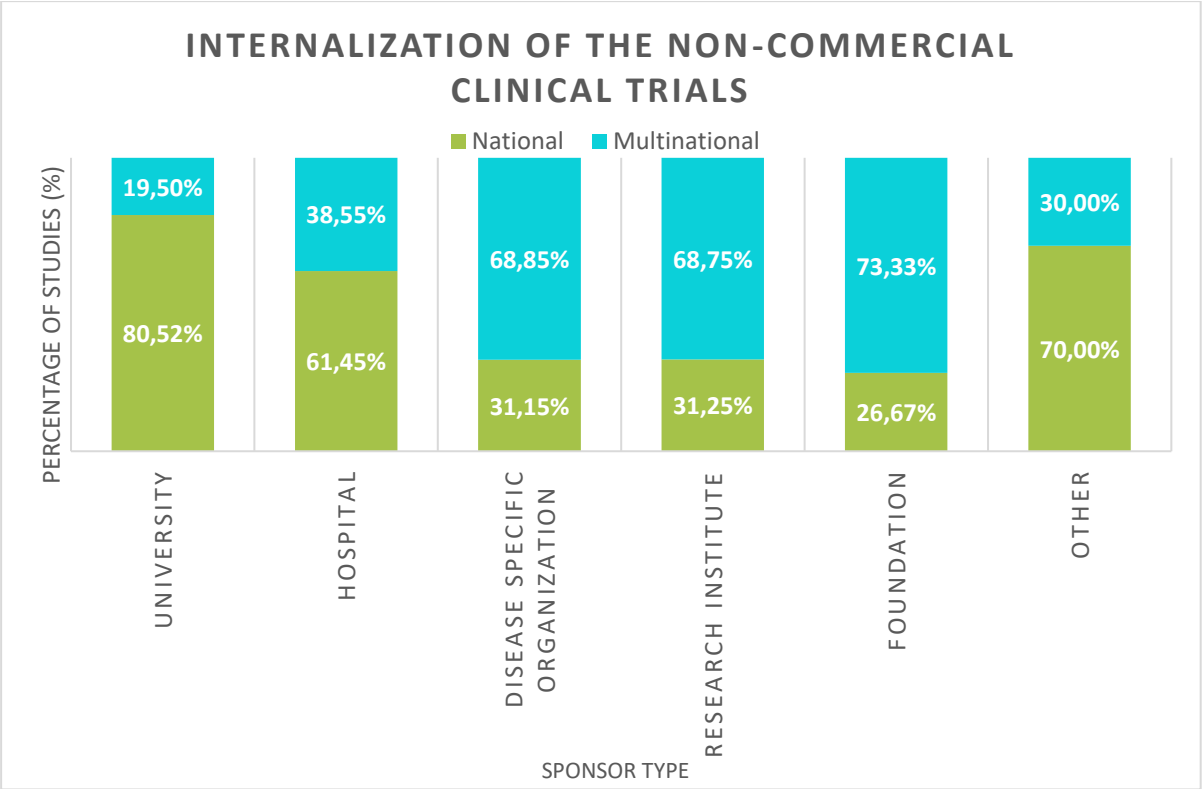

Figure 15: National or multinational non-commercial trials according to the sponsor.
Results are represented as the percentage of trials (%). National Studies are represented by the color green and multinational studies by the color blue. Other types of sponsor include clinics and government organizations.

4.2.4 Funders and Funding Agencies supporting Non-Commercial Clinical Trials

Taking into account the funder type of the non-commercial trials, non-profit funders are the leaders, funding 70.50% (n= 239) of the clinical trials (Figure 16A). According to the results, a total of 66 trials were supported by funding agencies, of which 40 were international agencies and 24 national ones (Figure 16B). The national funding agencies supporting non-commercial clinical trials are Fundação para a Ciência e Tecnologia (FCT) and COMPETE (Table 6).

When analyzing the type of intervention applied in each study with the type of funding agencies, we can observe that international funding agencies mostly fund trials with medicinal products as intervention (n= 24) and national funding agencies mainly found behavioral interventions (n= 16) (Figure 16C).

Figure 16: Funders of non-commercial clinical trials.
(A) Type of funders represented by percentage of clinical trials (%), with N= 339; (B) Funding agencies represented by number of clinical trials (N). Total number of trials funded by funding agencies (N= 66); (C) Interventions of non-commercial clinical trials by funding agencies represented by the number of clinical trials (N).

Table 6: The national Funding agencies of non-commercial clinical trials represented as total number of trials (N).

National Funding Agencies

Agency	Nº of Trials
Fundação para a Ciência e Tecnologia (FCT)	23
COMPETE	6

4.3 Published Commercial clinical trials vs Non-Commercial

Taking into account the main goal of this research project of comparing the scientific impact of the commercial and non-commercial clinical trials with Portugal as sponsor or participating country, the first publications of results of each completed trial was assessed, according to the methodology described in Figure 6. Within the 1402 Commercial Clinical trials, 970 are completed and of them, 280 have their results published in the scientific literature with only 24 having the authorship of national investigators (Figure 6, Figure 17). On the other hand, from the 339 Non-Commercial Clinical trials, 170 are completed, of which 54 have their results published and 38 have Portuguese authors (Figure 6, Figure 17). In terms of percentage, is it important to acknowledge that, in fact, only 28.87% of the commercial clinical trials publish the results and a slightly higher percentage (31.76%) of non-commercial clinical trials publish their results. Moreover, 70.37% of the non-commercial trials published have Portuguese authors while only 8.57% of the published commercial clinical trials have Portuguese authorship.

From this chapter on, the analysis regards the published commercial and non-commercial clinical trials.

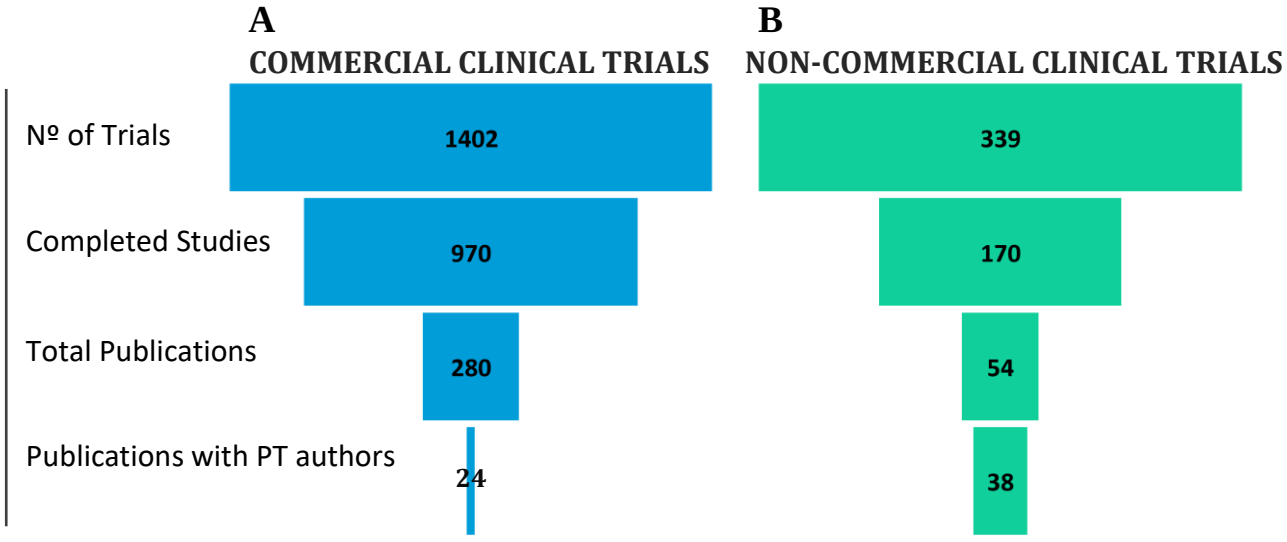

Figure 17: The number of Commercial and Non-Commercial Clinical Trials, completed, published and published with Portuguese (PT) authors.
(A) Results regarding commercial clinical trials. (B) Results regarding non-commercial clinical trials.

4.3.1 Time spent from the end of a clinical trial to publication of the results

When it comes to the time spent from the conclusion of the clinical trials to the publication of their results in the scientific literature, the time goes from several months to 10 years. Commercial clinical trials (n= 186; 66.43%) and non-commercial clinical trials (n= 30; 55.56%) most often take two years or less to be for non-commercial ones. Eighteen commercial clinical trials (6.43%) took more than four years to publish the results while only 2 non-commercial trials took the same time (3.70%). Data shows that the papers with Portuguese authors follow the same trend as described above (Figure 18A-B).

Considering the average time spent from the completion of the clinical trial to the publication of the results, represented as the average time in years, no significative differences ($p > 0.05$) were observed between non-commercial trials (2.13 ± 0.21 years) and commercial clinical trials (1.82 ± 0.10 years) (Figure 18C). Moreover, considering only non-commercial clinical trials with Portuguese authorship, the time to publish (2.38 ± 0.24 years) is also not significantly different from the average time spent for commercial clinical trials to be published with Portuguese authorship (1.96 ± 0.31 years) (Figure 18C).

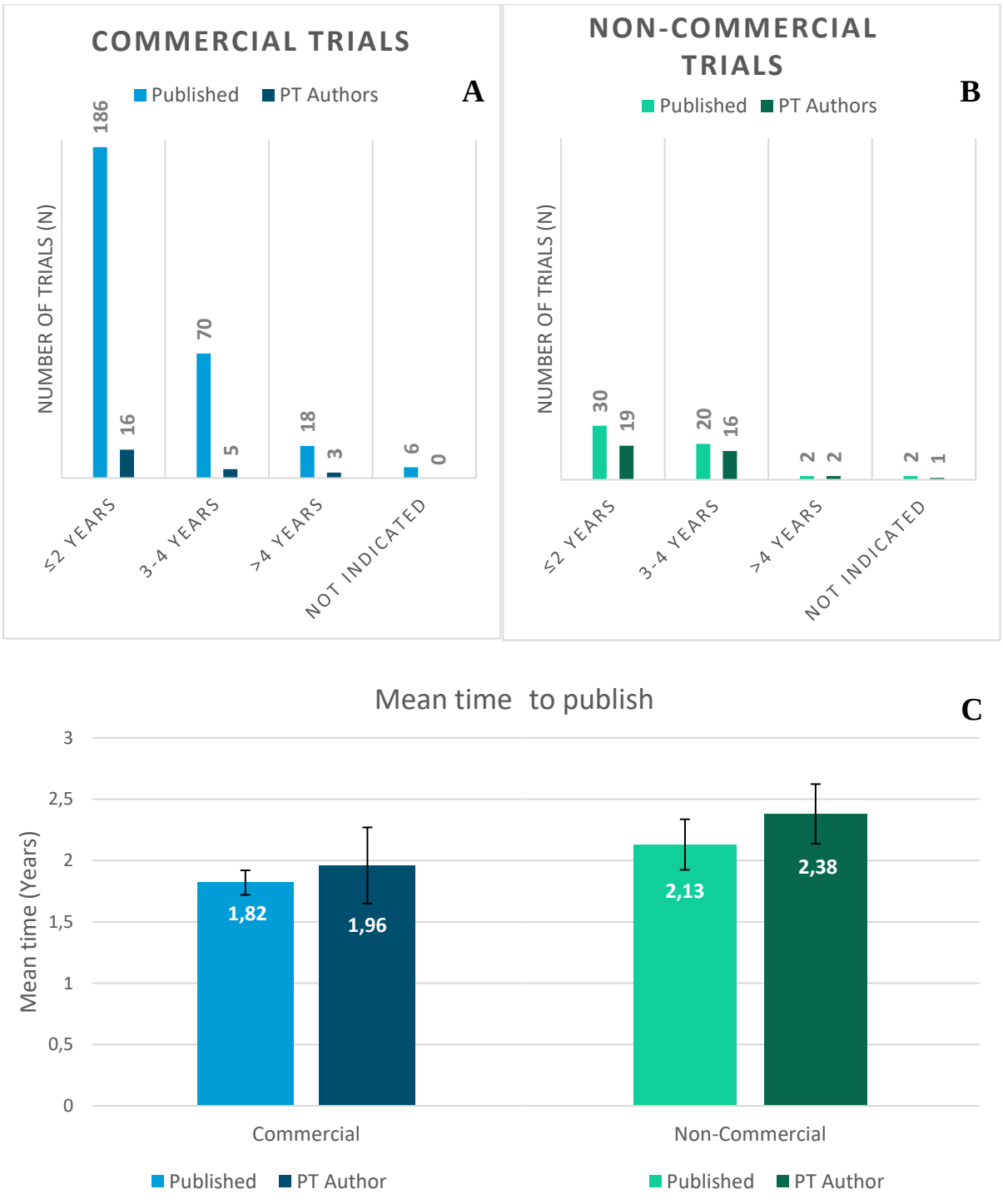

Figure 18: Time spent from completion of both commercial and non-commercial clinical trials to publication of the results.
(A) Results categorized in less than 2 years to publish; 3 to 4 years to publish and more than 4 years to publish for commercial clinical trials. Total of 280 published commercial clinical trials and 38 with Portuguese authors. (B) Results categorized in less than 2 years to publish; 3 to 4 years to publish and more than 4 years to publish for non-commercial clinical trials. Total of 54 published non-commercial clinical trials and 24 with Portuguese authors. (C) The average time spent to publish results both for commercial and non-commercial trials.

4.3.2 Therapeutic areas of interest in Published Clinical Trials

The most studied therapeutic areas from the trials that have their results published in the scientific literature are different when we are analyzing commercial and non-commercial clinical studies (Figure 19). In fact, within the commercial clinical trials, the area of greater interest is oncology (n= 58; 20.71% of the trials) and for the non-commercial clinical trials is cardiology/vascular diseases (n= 9; 16.67% of the trials). When we analyze the data from the articles with Portuguese authors, the scenario remains very similar.

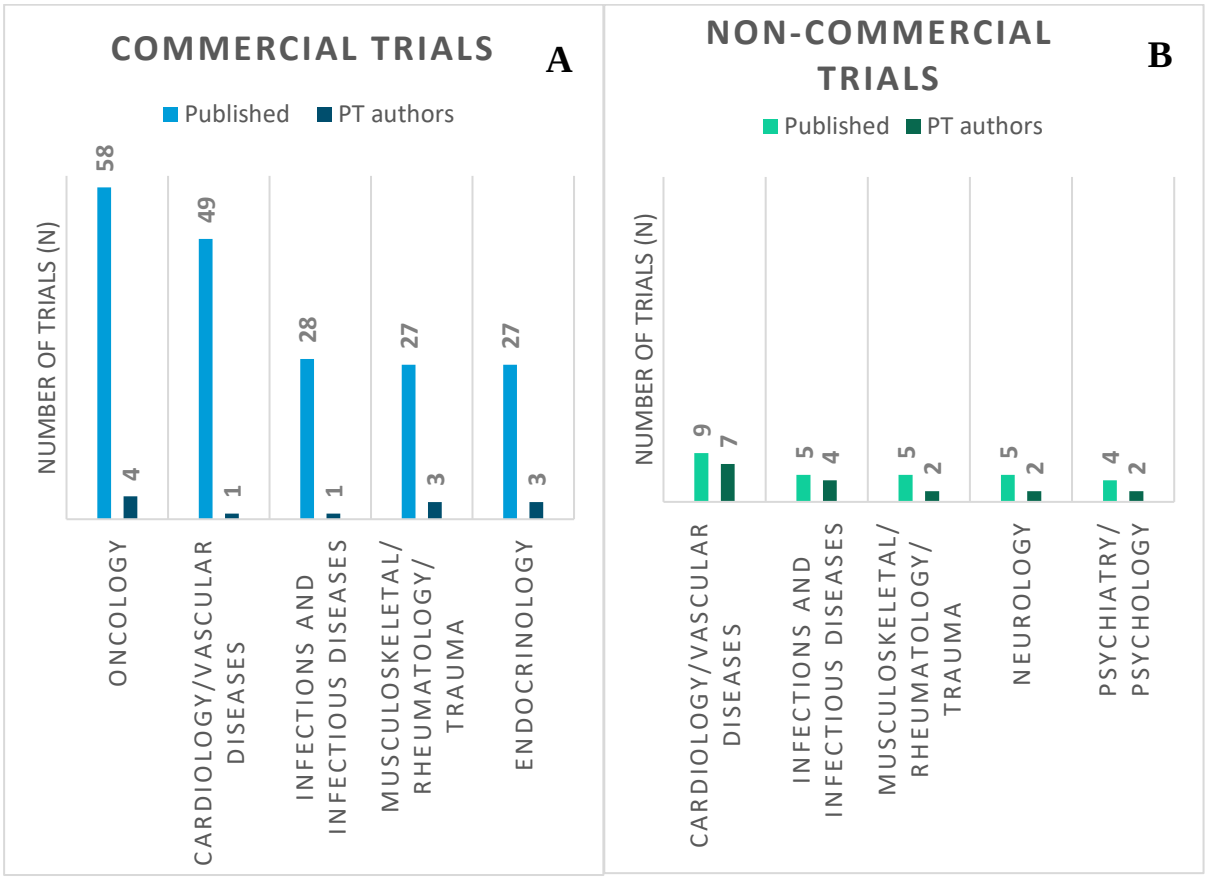

Figure 19: Number of the most studied therapeutic areas in the published commercial and non-commercial clinical trials including those with Portuguese (PT) authors.
(A) Results regarding commercial clinical trials. (B) Results regarding non-commercial clinical trials.

4.3.3 Interventions applied in Published Clinical Trials

The clinical trials that have their results published in the scientific literature mostly use chemical drugs as intervention (n= 184; 65.71%) or behavioral interventions (n= 17; 31.48%) depending on if they are commercial or non-commercial clinical trials, respectively (Figure 20). In the top three interventions focused on published trials, chemicals and devices are common

to commercial and non-commercial trials, while in the first biological/biotechnological drugs are considered (n= 87) and in the latter behavior trials (n= 17) were identified (Figure 20).

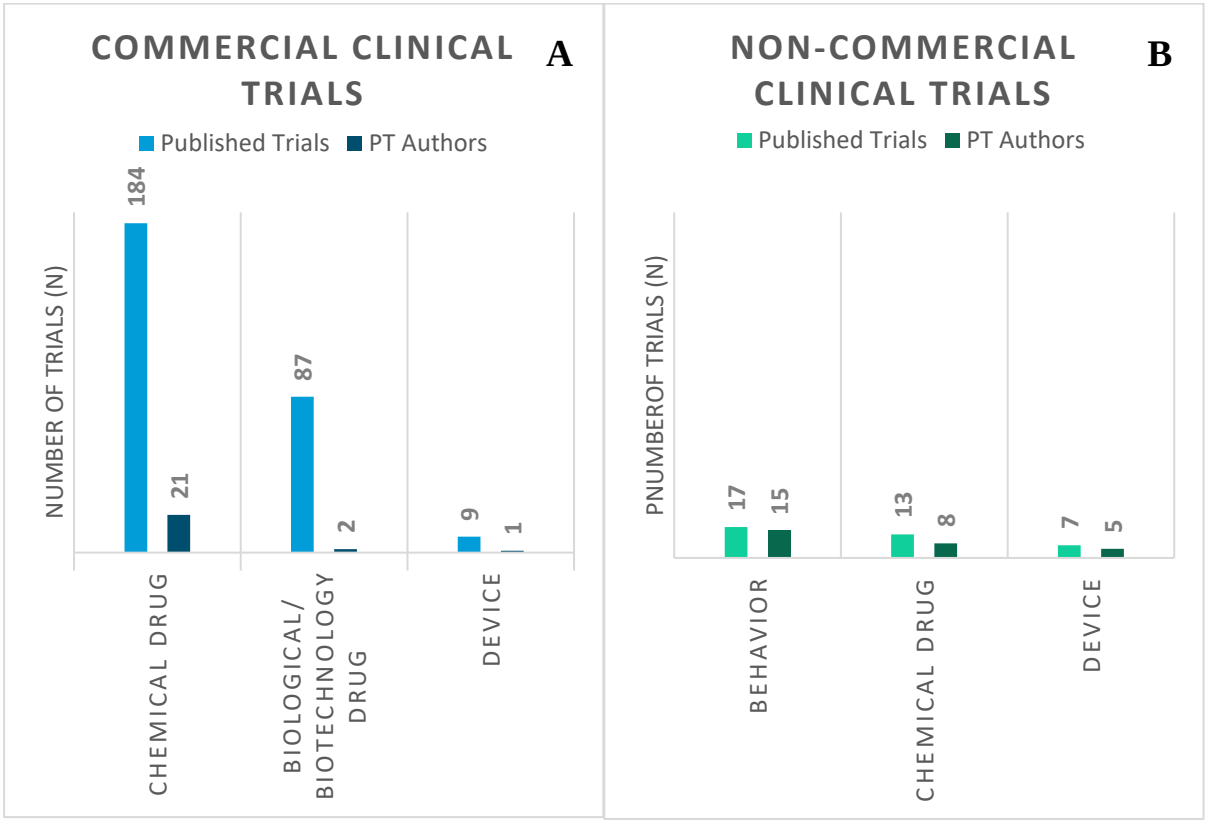

Figure 20: The main interventions applied in the commercial and non-commercial clinical trials that have their results published in the scientific literature.
(A) Results regarding commercial clinical trials. (B) Results regarding non-commercial clinical trials.

4.3.4 Sponsors of Published Clinical Trials

Considering the total number of published trials (n= 334), the pharmaceutical industry is the lead sponsor of published trials, sponsoring 83.83% (n= 280) of all clinical trials. After them, the universities and hospitals are the following sponsors, supporting 9.88% (n= 33) and 2.99% (n= 10) of the published clinical trials (Figure 21). Other types of sponsors like foundations, disease-specific organizations, and research institutes only support a residual percentage of the trials that have their results in the scientific literature. It is interesting to notice that although pharmaceutical companies are the lead sponsors of the published clinical trials, the set is not the same when considering the clinical trials that are published and have Portuguese authors. The universities surpass pharmaceutical companies when it comes to sponsoring clinical trials with publications with Portuguese authorship, supporting 43.55% (n= 27) of these published trials (Figure 21).

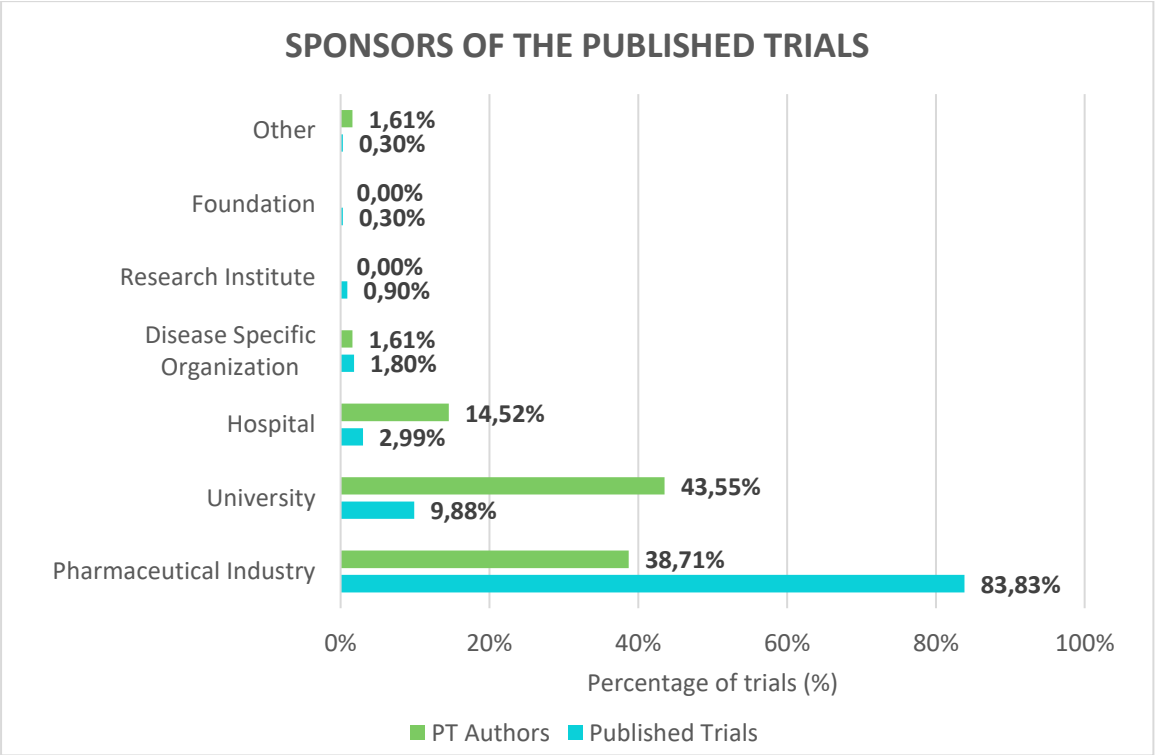

Figure 21: Percentage of published trials by Portuguese authors and by sponsor type (N= 334).

Countries sponsoring clinical trials that have their results published, identified in this work, show three top countries for both commercial and non-commercial clinical trials.

For the commercial clinical trials, the country sponsoring the greater number of clinical trials that reach publication is the USA, as they sponsor 66 trials with publication of results (23.57%). Succeeding, Switzerland is the second country promoting clinical trials with publication of results (sponsor of 49 trials, 17.50% of the published trials). At last, Germany sponsors 34 trials that reach publication in the scientific literature (12.14%) (Figure 22). It is relevant to notice that Portugal only appears in the sixth place, sponsoring 21 commercial clinical trials with the results published (7.50%) (see Appendix A 8)

When considering data on non-commercial clinical trials, the scenario is not the same. The country sponsoring the majority of completed published clinical trials is Portugal, as it sponsors 33 trials (61.11% of the published non-commercial clinical trials). Following, the UK sponsors 5 trials (9.26%) and France promotes 4 trials (7.41%) (Figure 22). In contrast, the USA only sponsors 2 non-commercial clinical trials that achieve publication of results (3.70%) (see Appendix A 8).

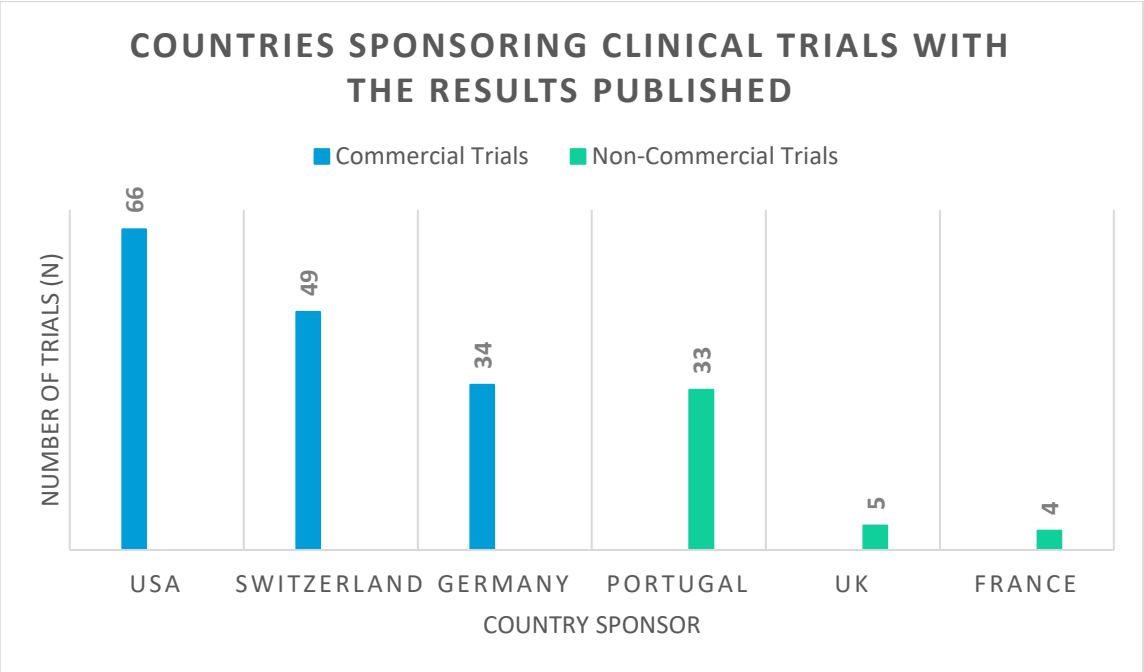

Figure 22: The top three countries sponsoring commercial clinical trials (left) and non-commercial clinical trials (right). Results represented as the total number of trials (N).

4.3.5 IFs measures of trial's publications

The Impact Factor (IF) of the journals where the results of the Clinical trials are published was obtained as described in section **1.7**. The IFs were divided into three groups of values to facilitate the analysis: IF≤5, 5<IF<20 and IF≥20.

Commercial clinical trials are well distributed among the groups of values of the IFs. Although a higher number of studies are published in journals with IFs higher than 20 (n= 105; 37.50% of the cases) (Figure 23A). On the other hand, non-commercial clinical trials mostly have publications with an IF lower than 5 (n= 29; 53.70% of the cases) (Figure 23B). In fact, only a small percentage of non-commercial clinical trials have an IF higher than 20 (n= 11; 20.37%).

Taking into account only the commercial and non-commercial clinical trials published in journals with IF higher than 20, some characteristics were assessed. Commercial clinical trials in this category are all multinational trials and 96.19% (n= 101) use medicinal products as intervention (63.81% are chemical drugs and 32.38% are biological/biotechnological drugs) (Figure 23C). In addition, only 5.71% (n= 6) of these trials have Portuguese authors in the publications. For the non-commercial clinical trials, these are all multinational trials and 54.55% (n= 6) of them are funded by international funding agencies (Figure 23C). Besides that,

72.73% (n= 8) of the trials use medicinal products as intervention (45.46% are chemical drugs and 27.28% are biological/biotechnological drugs) (Figure 23C). In addition, 18.18% (n= 2) of these trials have Portuguese authorship.

These results clearly show that non-commercial clinical trials achieve publications of lower IFs when compared to commercial clinical trials.

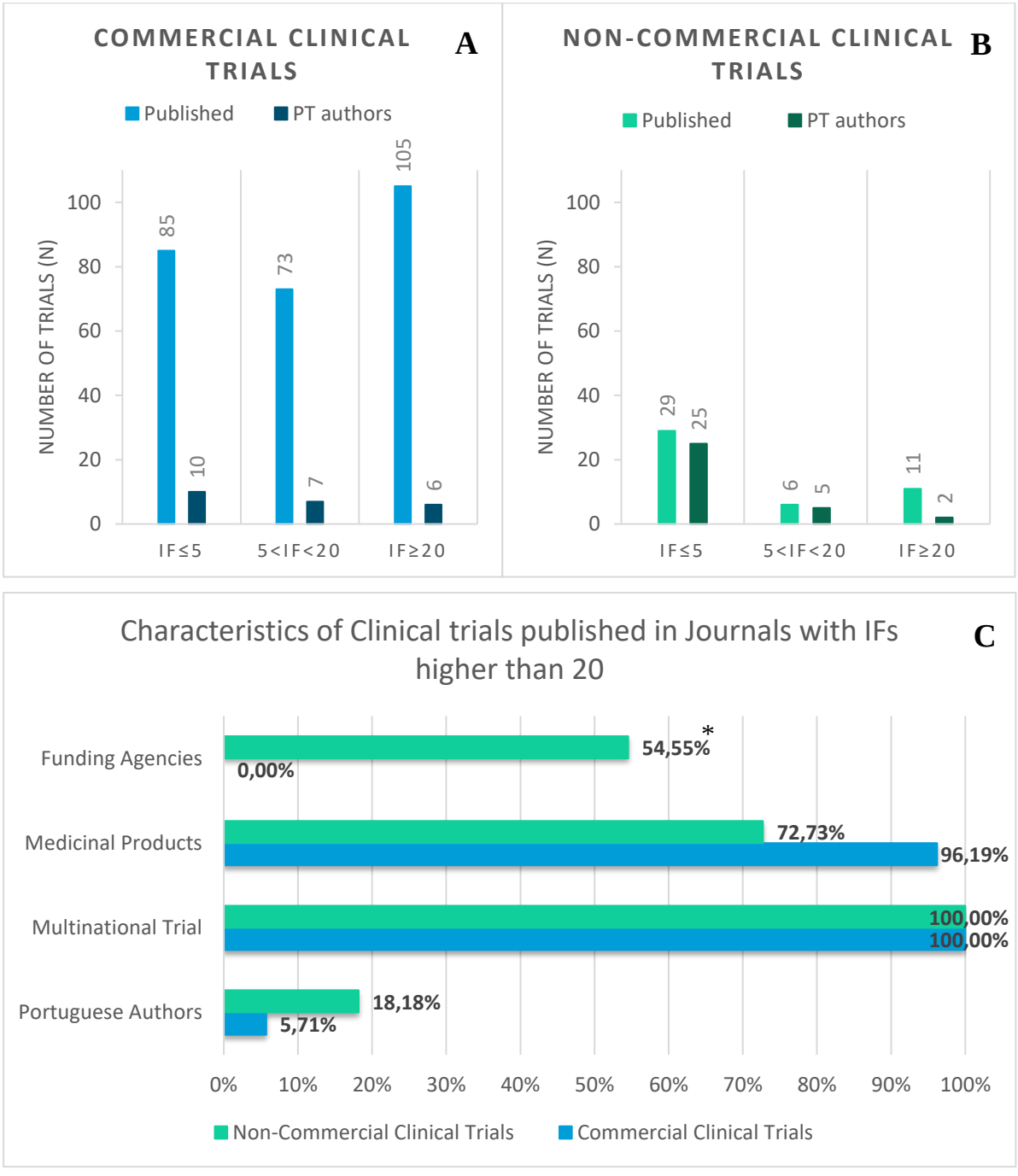

Figure 23: Commercial and Non-Commercial trials published in journals with IFs lower than 5, between 5 and 20 or higher than 20.

Trials published in 2019 were not considered. (A) Results for the commercial clinical trials. (B) Results for the non-commercial clinical trials. (C) Results for both commercial and non-commercial clinical trials regarding the characteristics of the clinical trials published in journals with impact factor higher than 20 (105 commercial clinical trials; 11 non-commercial clinical trials). * Only International funding agencies were identified for the Non-Commercial clinical trials.

When analyzing the mean of the publications IFs, it is possible to observe some divergence between commercial and non-commercial clinical trials and even if the publications have Portuguese authors or not (Figure 24). Publications of Commercial clinical trials have a statistically significant higher mean of IFs (21.65 ± 1.33) and published non-commercial clinical trials have a lower mean of 15.63 ± 3.27 ($p < 0.05$). When publications with Portuguese authorship are considered, commercial clinical trials have a mean of IFs of 17.09 ± 4.80 and non-commercial trials of 6.42 ± 1.93 that is also statistically different ($p < 0.05$). Additionally, there is no statistical difference between published commercial trials and with Portuguese authorship or between published non-commercial trials and with Portuguese authorship.

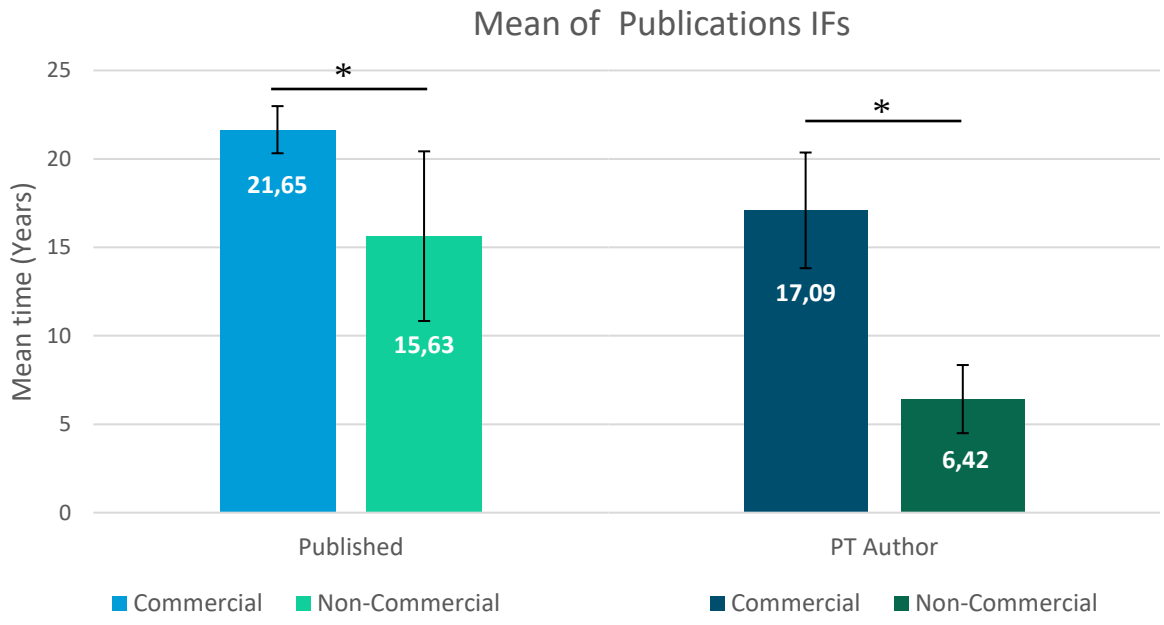

Figure 24: Mean of the IFs of the published clinical trials. Trials published in 2019 were not considered (*$p<0.05$).

Crossing the information of the clinical trials that are published in journals with an IF higher or equal to 20, with the therapeutic areas of concern studied in those clinical trials, it is possible to acknowledge the top four therapeutic areas of matter.

In the commercial clinical trials published in journals with an IF≥20, Cardiology/Vascular Diseases have a higher number of studies (33.96%) followed by Oncology (21.70%), Infectious Diseases (11.32%) and Neurology (10.38%) (Figure 25).

For the non-commercial clinical trials that have their results published in journals with an IF≥20, the most studied therapeutic area is Infectious Diseases (27.27%), followed by Neurology and Oncology (18.18% each) (see Appendix A 5 to see all the therapeutic areas). Relatively to Cardiology/Vascular Diseases, only 9.09% of the publications with an IF greater than 20 study this therapeutic area (Figure 25).

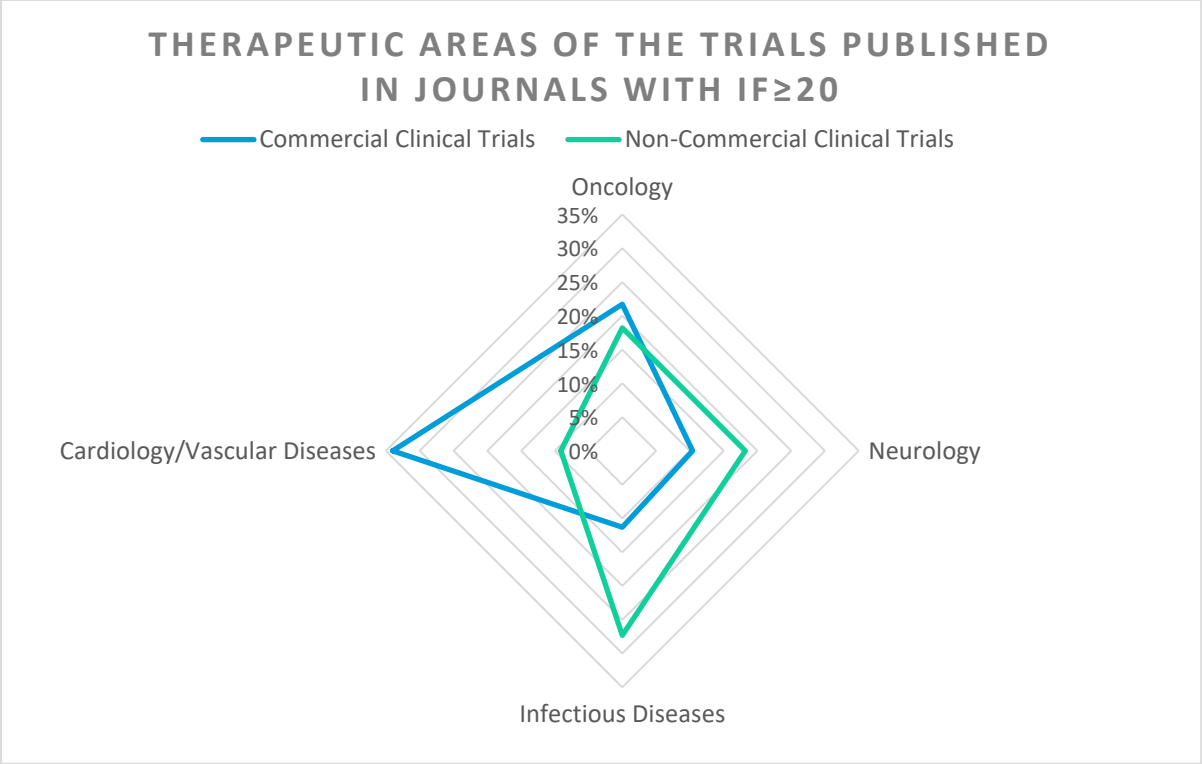

Figure 25: Representation of the therapeutic areas of the trials published in journals with IF≥20. Results are represented as the percentage of publications (%).

4.3.6 Quartile measures of trial's publications

According to the data derived from this study, both commercial and non-commercial trials generate publications within the Quartile 1 (Q1) (n= 210; 75.00% of the commercial trials and n= 30; 55.56% of the non-commercial ones) (Figure 26A-B). Besides that, there are no

publications with a Q4 for the non-commercial clinical trials (Figure 26B) and only 0.71% (n= 2) of the commercial clinical trials have publications within this quartile (Figure 26B).

When analyzing the therapeutic areas of concern for the clinical trials that are published in journals with a Journal Impact Factor (JIF) Percentile of Q1, the results were similar to those shown in Figure 25 (publications in journals with IF higher than 20).

Hereupon, an assessment of the therapeutic areas of concern in clinical trials that are published in journals that achieve a Journal Impact Factor (JIF) Percentile of Q2 for middle-high position (between top 50% and top 25%) and Q3 for middle-low position (top 75% to top 50%), was performed. Percentile of Q4 was not assessed once the number of publications was extremely low and it does not bring relevance or solidity to the investigation (only 2 commercial clinical trials and 0 non-commercial clinical trials were published in journals with a percentile of Q4).

In fact, for the commercial clinical trials that are published in these journals, the therapeutic areas associated are mostly related to oncology studies (n=11; 22.00%) and Musculoskeletal/Rheumatology/Trauma (n= 9; 18.00%) (Figure 26C). Relatively to the non-commercial clinical trials the scenario is different. Psychiatry/Psychology is the principal therapeutic area of the clinical trials that have their results published in journals with a JIF percentile of Q2 or Q3 (n= 3; 18.75%) and Musculoskeletal/Rheumatology/Trauma, Occupational/Eating habits/Sports/Sleep and Neurology follow with a percentage of 12.50% (n= 2) each (Figure 26C).

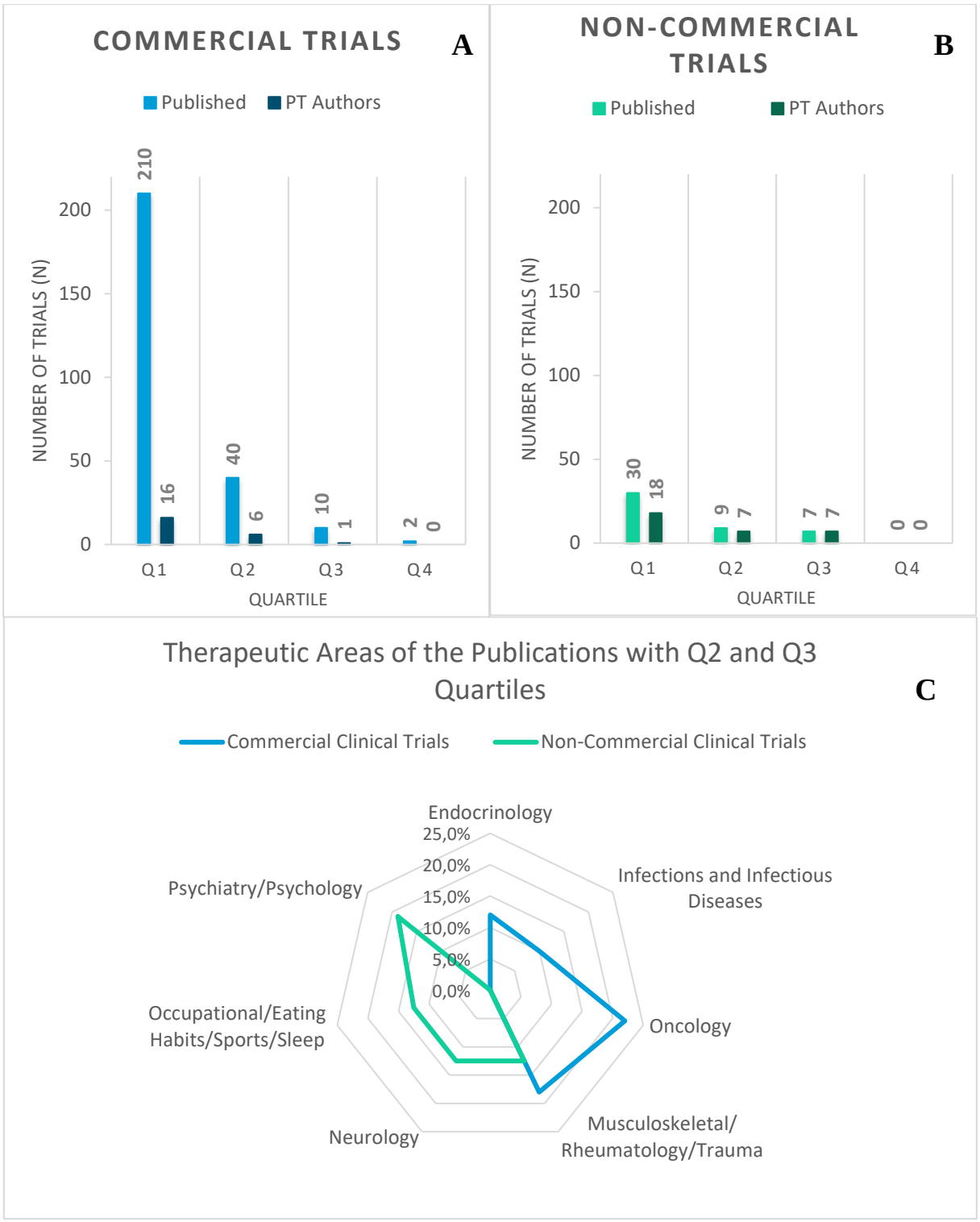

Figure 26: Quartiles of the publications generated from the clinical trials.

(A) Division of the commercial clinical trial publication's per Quartile (Q1 to Q4) represented as the number of trials (N). (B) Division of the non-commercial clinical trials publication's per Quartile (Q1 to Q4) represented as number of trials (N). (C) The therapeutic areas studied in the publications with Q2 and Q3.

DISCUSSION

For the first time, a systematic research has been conducted over the past fourteen years on four registration platforms that allowed us to characterize in detail the current situation of all interventional studies in Portugal. In addition, and also for the first time, it was possible to crosscheck and supplement the information from these records with the publications of completed studies resulting from these trials.

Overall, we found that while commercial studies are published in similar percentages to non-commercial ones, it is in the latter that we have identified more Portuguese investigators as authors.

Clinical Trials in Portugal

The first results obtained rely on the amount of commercial and non-commercial clinical trials. As it was expected, the total number of commercial clinical trials is considerably higher than the number of non-commercial trials. In fact, from the total of 1741 clinical trials that are in compliance with the inclusion criteria, 80.53% are commercial and 19.47% are non-commercial clinical trials.

Comparing these results with the annual evolution of the clinical research in Portugal published by INFARMED (that includes only clinical trials on medicinal products), the scenario is not surprising (see section **1.9**). As a matter of fact, in that work, the variation over the years of the percentage of commercial clinical trials in relation to the total amount of trials (including non-commercial) goes from 86.0% to 96.4% (Figure 5). However, non-commercial clinical trials considered in this work include all types of interventions and not only medicines, as it is considered in the data from INFARMED.

In order to compare directly the percentage of non-commercial clinical trials using medicines, in relation to the amount of trials with what was previously mentioned and also in the literature, 1343 commercial trials and 141 non-commercial clinical trials were found in this work. Therefore, herein the obtained proportion of clinical trials is 90.5% commercial trials and 9.5% non-commercial clinical trials which is slightly higher when compared to the study previously published in 2016 [31], and in line with those published by INFARMED.

Furthermore, the situation described for Portugal in this study is similar to other countries. Ignacio Atal *et al*., describe that the proportion of industry-sponsored trials in relation to non-

commercial ones was about 60% in Western Europe countries [9] and a study with clinical trials from 2004 to 2015 reveals that IICTs only represent from 2% (in countries like Latvia and Poland) to 37% (in the Netherlands) of the clinical trials performed in each European country [31].

Regarding the publication of results in clinical trials, data shows that similar percentages of completed studies (commercial and non-commercial) were published in peer-review journals (28.87% vs 31.76%, respectively; Figure 17). The results achieved herein are different from those of other countries for commercial trials. A Spanish study reveals that 63.8% of commercial trials are published in peer-reviewed journals while the percentage for the non-commercial clinical trials is only 39.4% [7]. As in our work, we only considered the first publications of each completed study our results might be underestimated. However, our work is in compliance with other studies performed where the percentage of non-commercial clinical trials published was slightly higher than the commercial ones [50], [51].

Independently of the source of funding, authors may often not submit studies with negative findings because they anticipate rejection by journal editors [52]. Interestingly, studies of lower methodological quality are more likely to produce "positive" results and may, therefore, be more likely to be published [53].

These results are relevant once the publication of the results is strongly recommended by ICMJE and there is still a huge space to grow into a higher percentage of published trials [54]. Although the publication of results in medical journals may entail some difficulties, the ethical justification for the conduction of the clinical trials must be translated for the sharing of the results. In 2013, the declaration of Helsinki recommended the publication of all the results of clinical trials, including negative outcomes [55]. Additionally, this recommendation will become legally bound when the European Regulation for clinical research comes into force (Regulation EU 536/2014) [44].

Of note, as previously referred, Portuguese investigators are less likely to be part of the authorship in the commercial publications (8.57%) than in non-commercial ones (70.37%). The fact that only 8.57% of the commercial trials have Portuguese authorship reflects that although they were involved in patient recruitment, they did not contribute to the study or protocol design. On the other hand, Portuguese investigators are the authors of the largest number of non-commercial study papers (70.37%) which reflects their greater involvement in critical

study steps (study and protocol design) and not just as recruiters. This involvement of Portuguese investigators in non-commercial trials, either/both as sponsor-investigator or/and investigators, certainly contributes to a general capacitation of the clinical team in clinical studies.

Support for and facilitation of the qualification, training, and infrastructures required for implementing academic clinical trials are key elements of the success of clinical research, therefore for the deep involvement of the investigators [36], [56]. Additionally, a study revealed that providing scientific mentorship for coordinators and investigators, regulatory guidance statistical resources and manuscript support to assist investigators in the development and implementation of research ideas, increases first author publications [57].

To turn Portugal more competitive in clinical trials, there are some steps that should be taken. The APIFARMA annual report [32] outlined some initiatives that should be implemented by 2021 and which are expected to increase Portugal's competitiveness and the involvement of Portuguese investigators in the design and conduct of clinical studies. There are therefore several measures like: ensure funding for the development and capacity building of national health service infrastructures; promote Portugal and investigators abroad; create a uniform financial contract basis; develop guidelines for the establishment of support structures for clinical research in health facilities; enhance clinical research activities for career advancement and streamline and monitor the integration and optimization of different information systems.

Sponsors and Funders

Getting to know the nations responsible for sponsoring the clinical trials included in this research project enlightens us on the pipeline for therapeutic discover developed in each country. The USA is the main sponsor of commercial clinical trials as they promote 29.88% of the commercial clinical trials with Portugal as a participating country (Figure 9). On the other hand, they only support 3.70% of the non-commercial clinical trials (see Appendix A 8). These results suggest that United States clinical research is largely controlled by the economic interests of the pharmaceutical industry. Considering the case of Portuguese organizations as sponsor, it is clear that our investigation is sponsor-driven by the academy. In fact, 215 trials with Portugal as sponsor country are sponsored by non-commercial institutions while only 111 trials are industry-sponsored (Figure 9, Figure 13).

Within the 1402 commercial clinical trials, 100% of the sponsors are pharmaceutical industries. Analyzing the type of sponsors in the non-commercial trials, it is notable that, universities are the main supporters (154 in 339 trials, 45.43%) as academic researchers are the main responsible for initiating clinical studies of non-profit organizations (Figure 11). Similar results have been published for non-commercial clinical trials in Portugal where 139 out of 282 trials (49.29%) were sponsored by universities [28].

A clinical trial can be performed in several countries (multinational) or in a single country (national). This information was crossed with the sponsor type of the clinical trials. Data shows that universities and hospitals most frequently sponsor clinical trials implemented only in Portugal (80.52% of the times and 61.45%, respectively), while disease-specific organizations, research institutes, and foundations sponsor a higher number of multinational non-commercial trials (68.85%; 68.75% and 73.33% of the times, respectively) (Figure 15). For the pharmaceutical companies, all the trials are multinational.

According to several authors, international collaboration in clinical trials offers numerous advantages for the generation and interpretation of evidence and also plays an important role in reducing waste in health research [56], [58], [59]. Nevertheless, the multinational collaboration in clinical trials is constrained by scientific, ethical, economical, operational, and regulatory considerations [9]. Different sponsors may have different capacities to address these constraints and data shows that universities and hospitals are in disadvantage when compared to the other non-commercial organizations but especially when compared to the pharmaceutical industry.

In the 339 non-commercial trials, 30 (8.85%) were funded by for-profit organizations and 49 (14.45%) both by for-profit and non-profit organizations. In these cases, the ownership of the trial may raise some doubts. Even though this support may be money or other type, it is not clear if the owner of the obtained results is the sponsor (non-commercial organization) or the funder (for-profit organization) [28]. In fact, CTRs do not have this information and if the owner is, in fact, the for-profit organization, the trial is not a non-commercial trial but a commercial one.

Considering the funding agencies, within the 339 non-commercial clinical trials, 68 were funded by funding agencies, of which 40 were international agencies, 24 national ones and 2 were both national and international agencies (Figure 16B).

Only two distinct national funding agencies supported non-commercial trials – FCT and COMPETE (Table 6). Other studies have described similar results where only a small percentage of non-commercial trials (18%) were funded by funding agencies [28]. Within the national funding agencies, behavioral interventions are the most applied while medicinal products are mostly used in trials funded by international funding agencies (Figure 16C). These results reinforce that funding for non-commercial clinical trials still needs to be improved in Portugal. In fact, to be able to do so, non-commercial organizations that wish to act as sponsor in clinical trials should invest in the development of adequate legal, administrative and management skills, just as they do for scientific skills [27]. ECRIN and its members work with the goal of providing this managing support for non-commercial trials. In general, CTUs can help organizations and investigators to improve the quality and support of non-commercial clinical trials since the idea until the close-out of the studies [9], [31], [36].

When it comes to the main sponsors of the published clinical trials, in a total of 334 trials with the results published in the scientific literature, 83.83% of them are industry-sponsored (16.17% being non-industry sponsored). Following, 9.88% of the trials are sponsored by universities (Figure 21). Remarkably, when analyzing the clinical trials published with Portuguese authors (total of 62 trials), the universities sponsor the majority of the trials (43.55%) while the pharmaceutical industry goes down for second place, sponsoring 38.71% of the trials that have their results published with Portuguese authors. On the other hand, other authors have shown that commercial sponsors are responsible for higher percentage of publications, - [49], [50], [60] – but as above mentioned, our study only considers the first publication of completed trials. Additionally, the obtained percentages in this work are for the first time-based in publications authored by investigators from a specific country, and the other studies do not narrow the inclusion criteria to this requirement.

Types of Interventions

Medicinal products include both chemical and biological/biotechnological drugs and are the main interventions applied in commercial and non-commercial clinical trials in Portugal (Table 7). As expected, behavioral interventions only exist in non-commercial clinical trials (26.84% of non-commercial trials) (Figure 12). Clinical trials with behavior interventions are cheaper and easier to perform once the regulations are less demanding and the financial investment is considerably lower than the one needed in medicinal products as intervention.

Accordingly, non-commercial sponsors can perform these clinical trials without so many difficulties.

Relatively to the type of interventions described in published studies, chemical drugs are the most used in commercial clinical trials (65.71%) and behavioral intervention in non-commercial trials (31.48%) (Figure 20). These results are in accordance with the expected once chemical drugs are interventions associated with a mandatory and complex regulatory process and high funding while behavioral interventions are less demanding when it comes to the conduction of a trial, therefore easier to carry out and publish. Additionally, commercial trials intend to request a marketing authorization at the end of phase III whereas in non-commercial trials unbiased comparative effectiveness trials with medicines are sought,

Table 7: The top three interventions for registered, published and published trials with Portuguese authorship.

	Commercial trials	**Non-commercial trials**
Registered trials	Chemical drugs (n= 880) Biological/Biotechnological drugs (n= 465) Devices (n= 52)	Chemical drugs (n= 99) Behavioral interventions (n= 97) Biological/Biotechnological drugs (n= 42)
Published trials	Chemical drugs (n= 184) Biological/Biotechnological drugs (n= 87) Devices (n= 9)	Behavioral interventions (n= 17) Chemical drugs (n= 13) Devices (n= 7)
Published trials with PT authors	Chemical drugs (n= 21) Biological/Biotechnological drugs (n= 2) Devices (n= 1)	Behavioral interventions (n= 15) Chemical drugs (n= 8) Devices (n= 5)
PT – Portuguese		

Considering only clinical trials for medicinal products, for the pharmaceutical industry-sponsored trials, phase III is the most common phase of drug development studied (n=928; 69.00%) (Figure 8). This phase of drug development is the most expensive, time-consuming and difficult trial to design and run and it is possible to notice that commercial sponsors are mostly developing clinical trials in this phase. These results are also in accordance with the data provided by INFARMED (see section 1.9), and reference [32]. By contrast, there are only 22 trials in Phase I, suggesting that the industry isn't supporting new drug developments in Portugal. These results have been reported for other countries like Spain where 47.2% of the approved drug trials were phase III and only 8.6% were phase I [7].

Moreover, although phase III trials are the most studied in the non-commercial trials that use medicinal products as interventions, it is important to notice that the main sponsors of these trials are disease-specific organizations (45.5% of the cases) (see Appendix A 10). These organizations are highly funded by the industry having favorable financial support to conduct these trials. Examples of disease-specific organizations that sponsor phase III are EORCT (European Organisation for Research and Treatment of Cancer) and AIBILI (Association for Innovation and Biomedical Research on Light and Image).

Therapeutic Areas

The therapeutic areas of concern in the commercial and non-commercial clinical trials vary weather the study is registered, published or published in journals with high impact factors (IF>20). The top three therapeutic areas for both commercial and non-commercial clinical trials are summarized in Table 8 below.

Considering the commercial clinical trials, there are few differences in the top three therapeutic areas for registered trials, published trials and trials published in journals with IF>20 (Table 8). In fact, oncology and cardiology/vascular diseases are always considered medical expertise of high interest in all the categories. The only difference is that, although neurology is one of the three most study therapeutic areas for the registered commercial clinical trials, the scenario is not the same for the published ones. Infectious diseases replace neurology and appear as one of the most study areas in the commercial trials that are published and published in journals of high IFs.

For the non-commercial clinical trials, it is interesting to notice that while oncology is the most study therapeutic area in the registered trials, surprisingly the number of studies published does not reflect that trend. Moreover, considering only publications of high impact factors, this area shows again as one of the most published. This observation may be due to the fact that oncology trials take longer times to be completed once the endpoints are mostly related to overall survival and progression-free survival [61], having only 21 out of 78 trials completed in Portugal. Furthermore, on-going trials in oncology, as these have generally a long duration might be published, but in this work, we did not consider those publications. In this work, from the completed trials we identified that only 4 were published, of which, 3 had positive results and were funded by both profit and non-profit organizations. Two of these were published in journals with IF≥20. These results, related to completed trials, might express the lack of

efficiency in the performance of oncology trials for non-commercial trials and the urgent need to improve the limited funds for the promotion of clinical research.

Table 8: The top three therapeutic areas for registered, published and published trials in journals with IF>20.

	Commercial trials	**Non-commercial trials**
Registered trials	Oncology (n= 351) Neurology (n= 148) Cardiology/Vascular Disease (n= 135)	Oncology (n= 78) Cardiology/Vascular Disease (n= 44) Musculoskeletal/ Rheumatology/Trauma (n= 31)
Published trials	Oncology (n= 58) Cardiology/Vascular Disease (n= 49) Infectious Diseases (n= 28)	Cardiology/Vascular Disease (n= 9) Infectious Diseases (n= 5) Musculoskeletal/ Rheumatology/Trauma (n= 5)
Published trials in journals with IF>20	Cardiology/Vascular Disease (n= 36) Oncology (n= 23) Infectious Diseases (n= 12)	Infectious Diseases (n= 3) Neurology (n= 2) Oncology (n= 2)
IF – Impact Factor		

Oncology is an area of high costs and requires large teams of people spanning numerous institutions [38]. Besides that, these are clinical trials of great logistics and cancer is one of the main causes of death around the world, estimating 9.0 million deaths in 2016 [50]. Not surprisingly, the data shows that the industry promotes a large number of oncology trials (n= 351; 25.04% of 1402 commercial clinical trials and n= 351; 81.82% of 429 trials in oncology) (Figure 7). The oncology therapeutic area is a worldwide matter of high incidence and the pharmaceutical industry has the means to provide bigger support for these trials both financially and logistically.

Non-commercial sponsors have a total of 78 trials concerning the area of oncology (Figure 11). It means that 23.01% (the majority) study this therapeutic area. Despite the characteristics of this therapeutic area described above, we must bear in mind that the absolute number of non-commercial oncology trials is considerably lower than that of commercial trials (4.5 times lower). Furthermore, within the 78 oncology non-commercial trials, 36 (46.15%) are sponsored by disease-specific organizations (see Appendix A 9). These organizations are largely funded by the industry, so financial support is facilitated.

Others have stated that there is no overall difference in the probability of publication of oncology trials, based on the type of sponsor [45], [62]. In fact, it is less likely to have papers published regarding their positive or negative results, instead of the sponsorship [62]. The scientific community interest level can be low and journals may believe that negative reports adversely affect their impact scores [63], [64].

Time to Publish and Scientific Impact

Considering the time spent from completion of a clinical trial to publication of results, it was confirmed with this work that the majority of trials take around 2 years to be published (Figure 18). This is the scenario for both commercial (66.43%) and non-commercial trials (55.56%). In fact, sponsorship (commercial vs non-commercial) demonstrates to be not significant for the time spent for the publication of results once the average for commercial trials is 1.82 ± 0.10 years and for non-commercial ones is 2.13 ± 0.21 years ($p > 0.05$) (Figure 18).

Other studies have assessed time to publication of results of clinical trials [65], [66], [67]. One of the studies involved clinical trials registered in ClinicalTrials.gov from 2007 to 2010 and sponsored by Academic Centers in the US. The results showed that the median time spent from completion of the trial to publication of results was 13.9 to 28.3 months, depending on the academic institution [65]. In fact, the results for non-commercial clinical trials obtained in this project (around 24 months) are within the range described in the above mention publications. Ionnidis *et al*., in 1998, assessed the median time to publication (calculated as the time spent from completion of the trial to publication od results) in 2.4 years [67]. The results are very similar to the median time estimated in this research project (1.8 years for commercial trials and 2.1 years for non-commercial ones). Moreover, the studies revealed that positive outcomes contribute to diminishing the median time for publication of results [66], [60]. These findings support the need for prospective registration of all trials to minimize publication bias as researchers should be encouraged to publish promptly the results of a trial irrespective of its results. The analysis of the influence of the trial's outcome influence was not performed in this study but in future projects it would be interesting to assess this information in trials performed in Portugal.

Taking into account the primary goal of assessing the scientific impact of the commercial and non-commercial clinical trials with Portuguese as institutions and/or as sponsor, an

individual approach to the journal's quality measure was performed. As mentioned in section 1.7, a higher JIF is deemed to be related to higher importance of the journal while publications are considered more relevant, in a specific area, when the Journals Quartile Percentile is Q1.

Considering the JIF of the journals where the trials results are published, the scenario is different for the commercial and non-commercial clinical trials. It is noteworthy that commercial clinical trials are more frequently published in journals with IF higher than 20 (37.50%) while non-commercial trials commonly publish in journals with IF lower than 5 (Figure 23). A study on the non-commercial trials performed in Portugal from 2004 to 2015 has shown similar results where the majority of the non-commercial trials were published in journals with an IF lower than 5 (84 out of 100 trials) [31].

Moreover, within the 105 commercial clinical trials with an IF greater than 20 and within the 11 non-commercial clinical trials with an IF higher than 20, some characteristics were assessed (Figure 23). All trials were multinational, and the majority of them used medicinal products as intervention. These results were expected once these trials contribute to global validation and gather valuable information for the improvement of health systems [9]. Furthermore, 54.54% of the non-commercial clinical trials with the results published in a journal with an IF higher than 20 were funded by an international funding agency, concluding that the financial support did not come from Portugal.

A total of 62 (n= 38 for non-commercial trials and n=24 for commercial ones) publications with Portuguese authorship were assessed. Not surprisingly, Portuguese investigators are more often the authors of the publications on the results of the non-commercial clinical trials, most probably because their involvement as investigators are valuable for the study and publication. Although Portuguese investigators are mostly authors in non-commercial trials, these are more likely to be published in journals with IF≤5 (n= 35; 56.45%) rather than journals with IF≥20 (n= 7; 11.29%).

The present work revealed that commercial clinical trials are usually published in journals with higher IFs when compared to the non-commercial clinical trials and the same happens for Portuguese authorship. The commercial and non-commercial sponsorship demonstrates to be statistically significant for the IF of the publication of results once the mean IF for published commercial trials is 21.65 ± 1.33 and for non-commercial ones is 15.63 ± 3.27 ($p < 0.05$). Moreover, the means IF are statistically different ($p < 0.05$) for Portuguese authorship once the

mean IF of journals where commercial trials with Portuguese investigators are published is 17.09 ± 4.80 and the mean IF respective to non-commercial trials is 6.42 ± 1.93 (Figure 24).

Concerning the second journal impact measure, the quartile, Q1 publications are deemed to be more relevant than Q2, Q3 and Q4 ones in the area of publication. Accordingly, the publications of both commercial and non-commercial clinical trials are predominantly published in Q1 journals (75.00% of the commercial clinical trials and 55.56% of the non-commercial ones) (Figure 26).

Summing up, there are clear differences in the scientific impact of the commercial and non-commercial clinical trials with Portuguese institutions as sponsors or/and participating country. This research project showed that the proportion of commercial clinical trials performed in Portugal is considerably higher than the non-commercial ones. Not surprisingly, the medical expertise and interventions applied in the clinical trials were different for the commercial and non-commercial sponsors. Orphan diseases, pediatric studies, and areas of lower incidence were part of the range of concern for the academic investigators and interventions with less regulation and legislation processes associated were more often studied (mostly behavioral interventions). By contrast, the pharmaceutical industry focused on worldwide diseases and high-cost interventions for their treatment (chemical drugs and biological/biotechnological drugs).

Moreover, although in Portugal a higher number of commercial trials are completed when compared to the non-commercial ones the percentage of publication is similar. In addition, the impact on the scientific community is deemed to be less relevant in non-commercial trials because publications from commercial sponsors achieve higher impact factors more often and publish about medical expertise that is considered the most prevalent and incident in the world. Nevertheless, the mean time spent from the completion of the clinical trials to the publication of results is similar for non-commercial and commercial clinical trials ($p < 0.05$).

The present study revealed that commercial sponsors publish in higher scientific impact journals when compared to non-commercial trials. As future perspectives, there is an urgent need to understand and overcome this setback once the information provided in non-commercial trials is extremely important and has a great impact on health policies. Besides that, the intervention of Portuguese investigators as main actors in the design of the clinical studies must be encouraged and supported. We expect that the results obtained with this work could be

used as a baseline for future assessment of clinical trials results in Portugal. It could also be used to reinforce the need for supporting national investigators not only providing funding to non-commercial trials but also empowering them in the conduct of clinical trials. This could be achieved by offering training opportunities in clinical trials methodology and good clinical practices, as well as stimulate/facilitate their participation in commercial and non-commercial trials. In this way, national investigators would probably be invited more often to participate in the design of commercial studies and also to participate in multinational consortia funded by European funds.

Limitations of the Study

Although the results accomplished in this research project are pioneer and raise relevant questions and answers, there are some limitations associated with the process. Firstly, it is important to notice that the baseline data is retrieved from the online clinical trials registries. This information is important to take into account once the information of clinical trials registered in the CTRs is filled usually by the sponsors of the trials and the accuracy is not 100% reliable. A recent study performed by PtCRIN showed that information upon the funders generated in these CTRs is still lacking in completeness and consistency [29]. Accordingly, data related to other fields is not always reliable and mostly not in accordance with the respective publication of results. Moreover, it must be noticed that in this research project the methodologic approach and inclusion criteria applied are extremely specific and the results generated are only related to the clinical trials and publications in accordance with the inclusion criteria. Some data, concerning the clinical trials excluded, may have been lost and were not analyzed.

Suggestions for Future Work

Considering the rates of publications, the first step of knowing the numbers of published commercial and non-commercial trials has been achieved in the present work. Further analysis should be conducted to understand the causes behind the number herein achieved. For example, the analysis of the influence of the trial's outcome influence, assessing the total number of protocol publications, or collecting the total number of citations of each paper would be a valuable analysis for the understanding of the clinical research in Portugal.

CONCLUSIONS

With this work, a clear picture of the clinical trials in Portugal is provided for the first time. The systematic search conducted in four international clinical trial registries and the information gathered from publications of completed studies allowed us to understand the level of involvement of Portuguese investigators in different types of clinical trials. It was a notable achievement to conduct this analysis in such a large number of clinical trials which implied an exhaustive methodological approach of approximately six months. In this way it was possible to assess the national scientific impact of each of the commercial and non-commercial clinical trials.

Based on the novelty of the obtained information, the major conclusions of this work are:

- Completed commercial and non-commercial trials are published in similar percentages (around 30%);
- The percentage of Portuguese investigators as authors is considerably higher in non-commercial trials publications when compared to those from commercial trials (70,37% vs 8.57%);
- Oncology is the therapeutic area of higher number of registered trials, but it is not the most targeted one in the publications of non-commercial trials. Moreover, oncology is one of the top three therapeutic areas for both commercial and non-commercial trials published in journals with an impact factor higher than 20;
- The average time from the end of a clinical trial to the publication of its results is 2 years both for commercial and non-commercial clinical trials;
- On average, commercial trials are published in journals with higher IF when compared to those from non-commercial trials (21.65 vs 15.63) and a higher difference is observed in publications with Portuguese authors (17.09 vs 6.42). Additionally, the differences deemed to be statistically significant ($p < 0.05$).
- Considering publications with Portuguese authorship, these are more likely to be published in journals with IF≤5 (56.45%) rather than journals with IF≥20 (11.29%).

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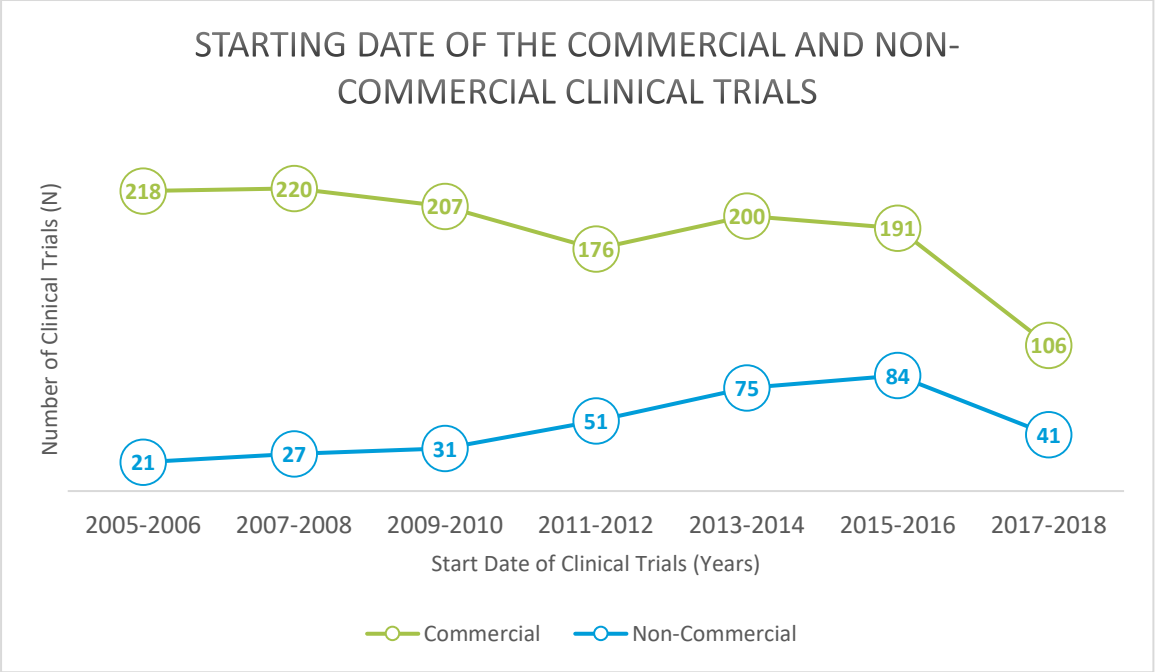
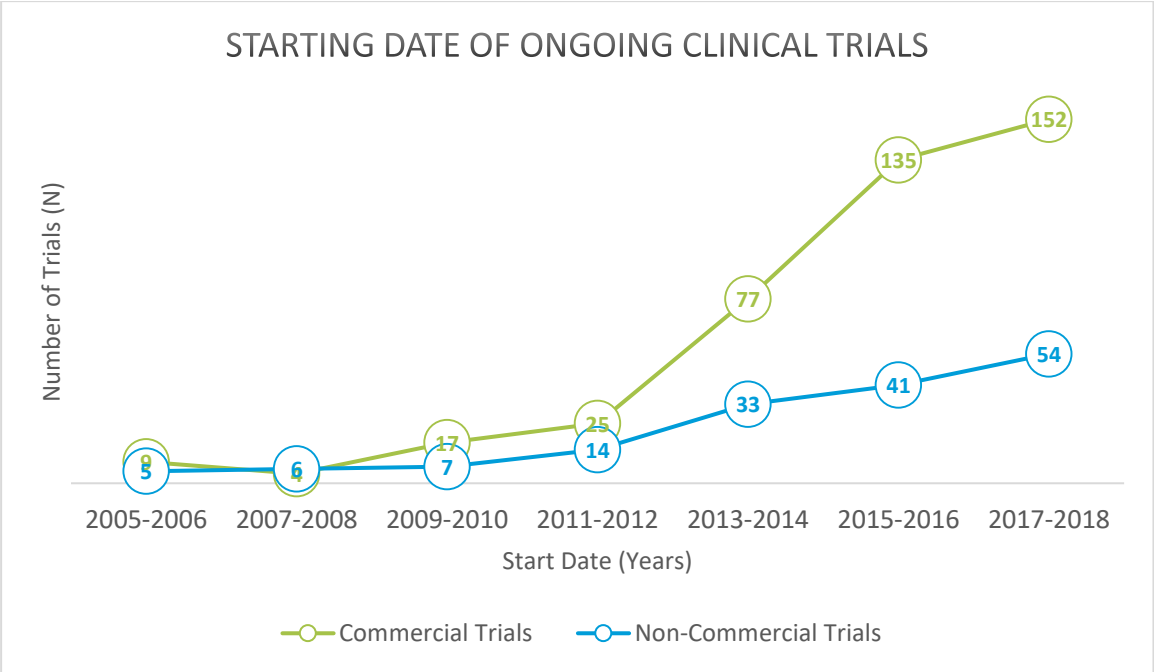
SUPPLEMENTARY INFORMATION



A 1: The starting date of the commercial and non-commercial clinical trials throughout the years (from 2005 to 2018). The results are represented by the exact number of trials starting in the correspondent year and the blue line represents the commercial trials while the grey line represents the non-commercial ones.

A 2: The therapeutic areas concerning the 419 Ongoing Commercial and 160 Non-Commercial Clinical Trials. Results represented as the total number of trials (N).

THERAPEUTIC AREA	COMMERCIAL TRIALS (N)	NON-COMMERCIAL TRIAL (N)
AGEING	0	2
ANESTHESIA	0	0
CARDIOLOGY/VASCULAR DISEASES	33	26
DENTAL OR ORAL HEALTH	0	6
DERMATOLOGY	3	0
ENDOCRINOLOGY	16	5
GASTROENTEROLOGY	36	2
GERIATRIC/REHABILITATION/NURSING CARE/ GENERAL PRACTICE	0	9
HEMATOLOGY	18	2
INFECTIOUS DISEASES	22	4
MUSCULOSKELETAL/RHEUMATOLOGY/TRAUMA	28	9
NEPHROLOGY	7	1
NEUROLOGY	34	8
OBSTETRICS/GYNECOLOGY	4	7
OCCUPATIONAL/EATING HABITS/SPORTS/SLEEP	1	3
ONCOLOGY	158	55
OPHTALMOLOGY	11	3
PEDIATRICS/NEONATOLOGY	22	6
PSYCHIATRY/PSYCHOLOGY	2	5
PULMONARY/RESPIRATORY DISEASES	21	4
UROLOGY	3	3
TOTAL	419	160



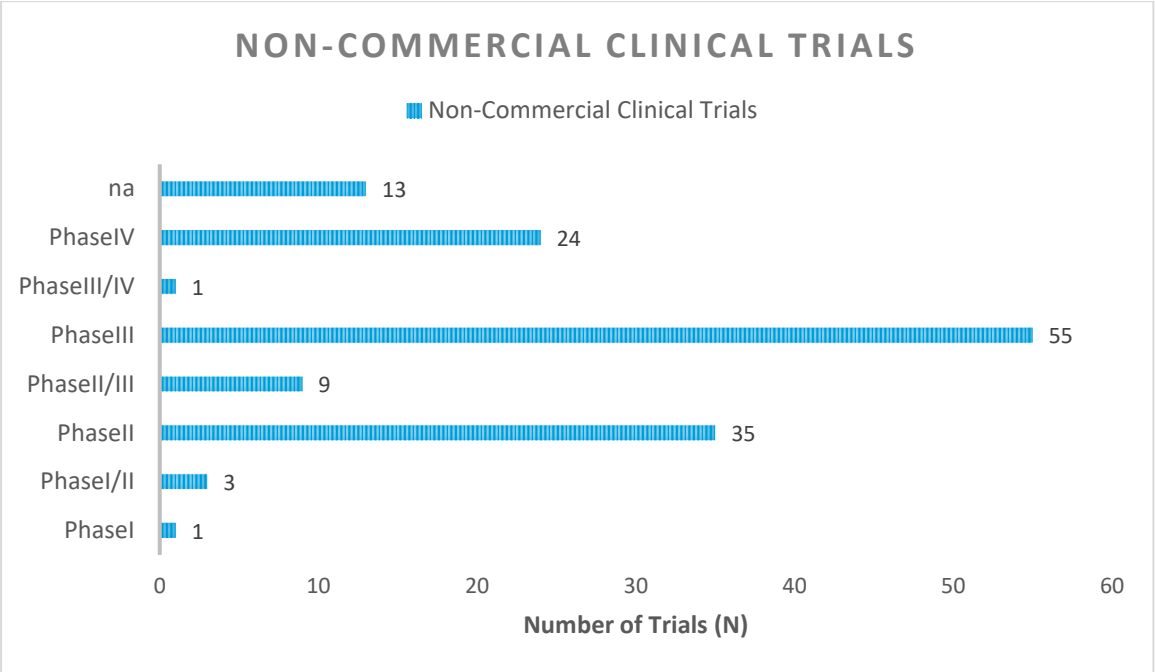
A 3: The starting date of the number of commercial and non-commercial clinical trials that are still ongoing. Evolution represented throughout the years by the total number of trials (N).

A 4: Representation of the therapeutic areas studied in interventional commercial clinical trials, starting from 1/10/2004 to 30/09/2018 with Portugal as participating country or sponsor. Results represented by the number of clinical trials and categorized as all the trials, completed trials, published trials and published trials with Portuguese (PT) authors.

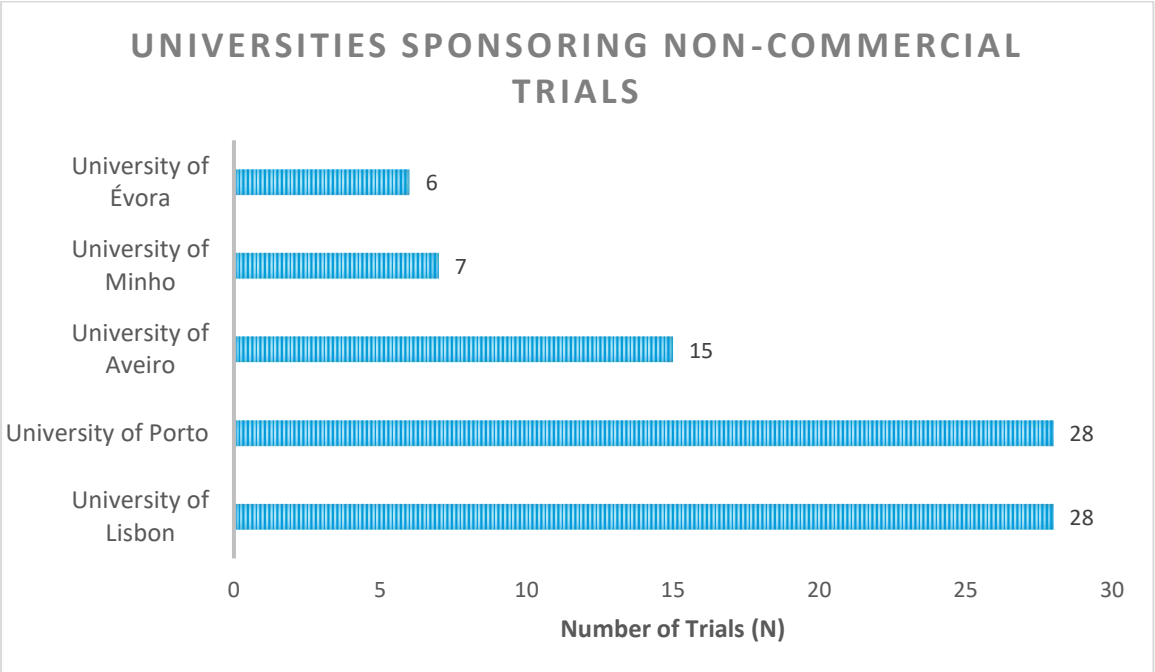
Commercial Clinical Trials	All Trials	Completed Trials	Published Trials	Published Trials with PT Authors
Ageing	0	0	0	0
Anesthesia	0	0	0	0
Cardiology/Vascular Diseases	135	101	49	1
Dental or Oral Health	1	1	0	0
Dermatology	22	18	2	0
Endocrinology	95	78	27	3
Gastroenterology	68	32	6	0
Geriatric/Rehabilitation/Nursing Care/ General Practice	1	1	1	1
Hematology	32	13	5	2
Infectious Diseases	123	101	28	1
Musculoskeletal/Rheumatology/Trauma	111	83	27	3
Nephrology	34	27	1	0
Neurology	148	113	25	6
Obstetrics/Gynecology	6	2	1	0
Occupational/Eating habits/Sports/Sleep	3	2	1	0
Oncology	351	192	58	24
Ophthalmology	74	63	6	1
Pediatrics/Neonatology	67	39	8	0
Psychiatry/Psychology	28	26	5	1
Pulmonary/Respiratory Diseases	76	54	23	0
Urology	27	24	7	1
TOTAL	1402	970	280	24

A 5: Representation of the therapeutic areas studied in interventional non-commercial clinical trials, starting from 1/10/2004 to 30/09/2018 with Portugal as participating country or sponsor. Results represented by number of clinical trials and categorized as all the trials, completed trials, published trials and published trials with Portuguese (PT) authors.

Non-Commercial Clinical Trials	All Trials	Completed Trials	Published Trials	Published Trials with PT Authors
Ageing	2	0	0	0
Anesthesia	7	5	1	1
Cardiology/Vascular Diseases	44	18	9	7
Dental or Oral Health	18	11	3	3
Dermatology	2	2	1	1
Endocrinology	14	9	1	1
Gastroenterology	8	5	2	3
Geriatric/Rehabilitation/Nursing Care/ General Practice	18	9	3	3
Hematology	3	1	0	0
Infectious Diseases	10	6	5	4
Musculoskeletal/Rheumatology/Trauma	31	22	5	2
Nephrology	3	2	0	0
Neurology	18	9	5	2
Obstetrics/Gynecology	11	4	2	1
Occupational/Eating habits/Sports/Sleep	15	12	3	3
Oncology	78	21	4	1
Ophthalmology	10	7	1	1
Pediatrics/Neonatology	20	13	3	2
Psychiatry/Psychology	9	4	4	2
Pulmonary/Respiratory Diseases	14	9	2	2
Urology	4	1	0	0
TOTAL	339	170	54	39



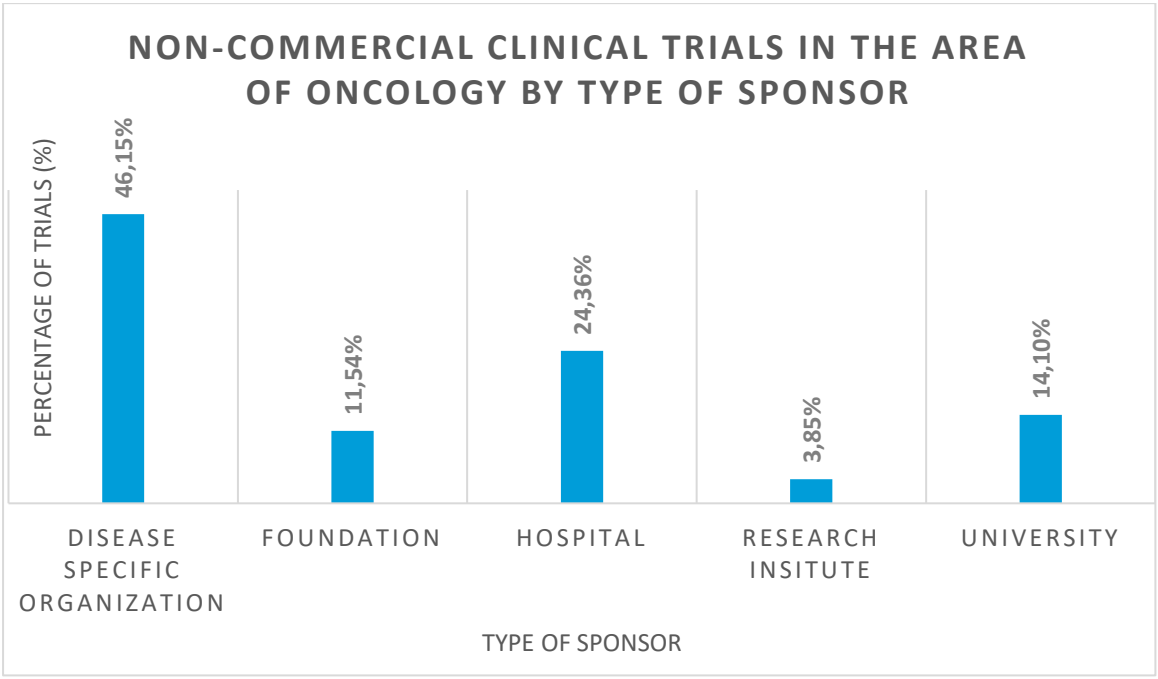
A 6: Phase of the trials considering non-commercial clinical trials with chemical drugs or biological/biotechnological drugs. The results are represented as total number of trials (N).



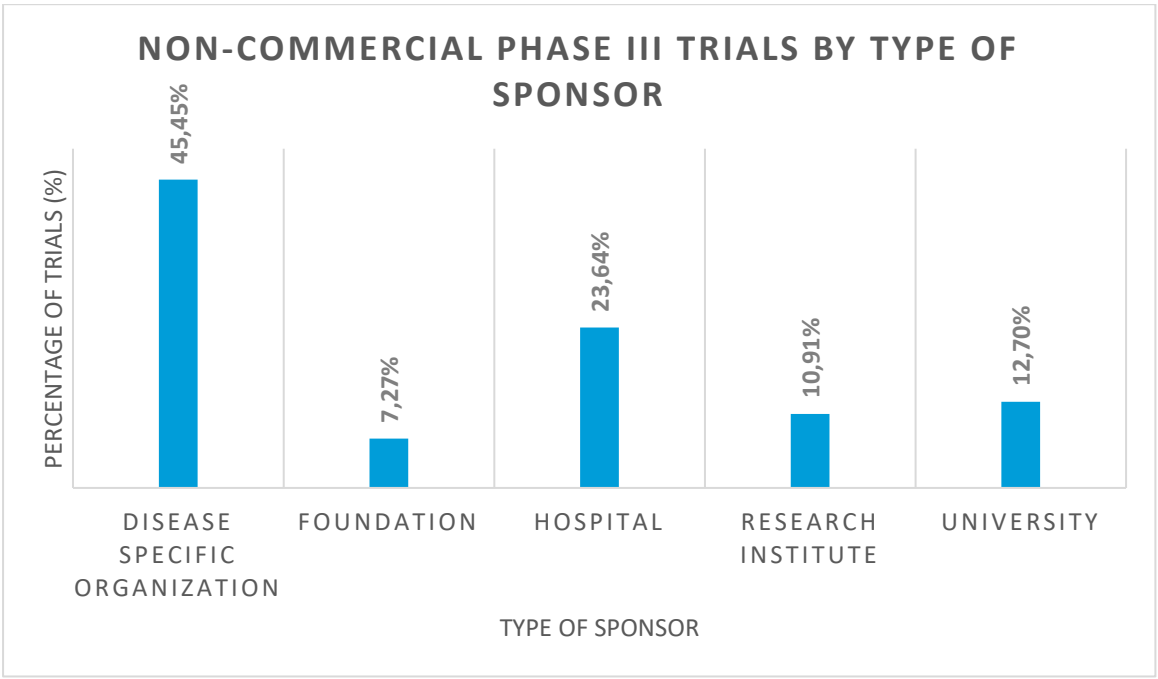
A 7: The principle Universities sponsoring the non-commercial clinical trials. The results are represented as the total number of trials (N).

A 8: Representation of the commercial and non-commercial clinical trials per country sponsoring the trial. Results are represented as total number of trials (N) and percentage of trials (%).

	Published Commercial Trials (N)	*Percentage of Published Commercial Trials (%)*	*Published Non-Commercial Trials (N)*	*Percentage of Published Non-Commercial Trials (%)*
Australia	0	0.00%	1	1.85%
Austria	0	0.00%	0	0.00%
Belgium	26	9.29%	0	0.00%
Canada	2	0.71%	0	0.00%
Czech Republic	0	0.00%	0	0.00%
Denmark	5	1.79%	0	0.00%
Finland	0	0.00%	0	0.00%
France	33	11.79%	4	7.41%
Germany	34	12.14%	0	0.00%
Ireland	0	0.00%	0	0.00%
Israel	1	0.36%	0	0.00%
Italy	1	0,4%	4	7.41%
Japan	0	0.00%	0	0.00%
Luxembourg	0	0.00%	0	0.00%
Netherlands	11	3.93%	2	3.70%
Portugal	21	7.50%	33	61.11%
Republic of Korea	1	0.36%	0	0.00%
Spain	2	0.71%	3	5.66%
Sweden	8	2.86%	0	0.00%
Switzerland	49	17.50%	0	0.00%
UK	20	7.14%	5	9.26%
Uruguay	0	0.00%	0	0.00%
USA	66	23.57%	2	3.70%
TOTAL	**280**	**100%**	**54**	**100%**



A 9: Representation of non-commercial clinical trials in the medical expertise of oncology (78 trials) by type of sponsor. Results presented as the percentage of trials (%).



A 10: Representation of non-commercial clinical trials concerning phase III of drug development (55 trials) by type of sponsor. Results presented as percentage of trials (%).