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ESTÁGIO EM MEDICAL WRITING NUMA CLINICAL RESEARCH ORGANIZATION

INTERNSHIP IN MEDICAL WRITING AT A CLINICAL RESEARCH ORGANIZATION

Relatório de estágio apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de mestre em Biomedicina Farmacêutica, realizado sob a orientação do Doutor Luís Veloso, Responsável do Departamento de Medical Writing da Eurotrials, Consultores Científicos, da Doutora Catarina Silva, Responsável do Departamento de Bioestatística da Eurotrials, Consultores Científicos, e da Professora Doutora Vera Afreixo, Professora Auxiliar do Departamento de Matemática da Universidade de Aveiro.

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palavras-chave

Medical writing, artigo científico, investigação clínica, publicação.

resumo

Este relatório tem como objetivo descrever a minha experiência durante os 9 meses de estágio curricular na Eurotrials, Consultores Científicos, como parte do 2º ano do Mestrado de Biomedicina Farmacêutica.

O estágio focou-se maioritariamente no desenvolvimento de competências e obtenção de experiência em atividades de Medical Writing, através da participação ativa em atividades usualmente desenvolvidas por medical writers: escrita, preparação e submissão de artigos científicos, preparação de pósters científicos, complilação de apêndices para Clinical Study Reports, e escrita de material educativo.

Durante o estágio, tive a oportunidade de adquirir conhecimentos essenciais relacionados com a atividade de Medical Writing, e de perceber de forma clara o seu papel na investigação clínica, como ferramenta essencial na interpretação, descrição e divulgação dos dados obtidos.

keywords Medical writing, scientific article, clinical research, publication.

abstract

This report aims at describing my experience uring the 9 months of curricular internship at Eurotrials, Scientific Consultants, as part of the 2nd year of the Master's in Pharmaceutical Medicine.

The internship was mainly focused on the development of skills and acquiring experience in Medical Writing activities, trought actively participating in activities usually developed by medical writers: writing, preparation and submission of scientific articles, preparation of scientific posters, compilation of appendices for Clinical Study Reports, and writing of educational material.

Throughout the internship, I had the opportunity to acquire valuable knowledge related to Medical Writing, as well as to clearly understand its role in clinical research, as an essential tool to interpret, describe and publish the data obtained.

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Abbreviations

BU	Business-unit
CRF	Case Report Form
CI	Confidence Interval
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CONSORT	Consolidated Standards of Reporting Trials
CRO	Clinical Research Organization
CSR	Clinical Study Report
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Publication Practices
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IF	Impact Factor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
RevMan	Review Manager
SOP	Standard Operation Procedure
STARD	Standards for Reporting of Diagnostic Accuracy Studies
STROBE	Strengthening of the Reporting of Observational Studies in Epidemiology
SU	Sub-unit

1. Introduction

This report is an overview of the 9-month internship as a Clinical Data trainee at the Medical Writing and Biostatistics Sub-Units (SUs) of Eurotrials, Scientific Consultants, which took place between September 2015 and May 2016. The internship was a part of the second year's curricular activities of the Master's Degree in Pharmaceutical Medicine by the University of Aveiro, Portugal.

As a Clinical Data trainee, I was actively involved in both medical writing and biostatistics activities, though my participation was considerably more frequent in the Medical Writing SU. In this document, I describe the tasks performed during the internship, as well as my objectives and overall evaluation of this training experience.

This internship was conducted under the supervision of Luís Veloso, Medical Writing Manager at Eurotrials Scientific Consultants, Catarina Silva, Biostatistics Manager at Eurotrials, Scientific Consultants, and Professor Vera Afreixo, Assistant Professor at the Department of Mathematics of the University of Aveiro.

1.1 Objectives

The objectives set for this curricular internship included:

- Primary objective:
    - To acquire knowledge and experience in the tasks associated with the projects and services falling under the scope of Medical Writing and Biostatistics.
- Secondary objectives:
    - To apply and build upon the knowledge acquired during the Bachelor's Degree in Biomedical Sciences and the Master's Program in Pharmaceutical Medicine.
    - To improve the soft skills needed to successfully work in a professional and team-based environment, such as communication skills, autonomy, proactivity, accountability and assertiveness.
    - To understand the functioning of a Clinical Research Organization (CRO) and their role in clinical research.

1.2 Report Structure

In addition to the introduction, this report is divided into five main chapters, briefly described below:

- **Chapter 2 – Overview of the host Institution**: describes Eurotrials, defining its role in the clinical research framework, its purpose, organization and services provided. The Medical Writing SU is described in more detail, as the majority of activities performed during my internship were related to this department.
- **Chapter 3 – State-of-the-art**: describes the state-of-the-art in clinical studies, CRO business, medical writing and the peer-review process.
- **Chapter 4 – Training experience:** describes the initial training period performed at Eurotrials, which provided the basis for the development of various practical activities, as well as the Medical Writing and Biostatistics activities performed throughout the internship.
- **Chapter 5 – Discussion**: provides a discussion of the main learning points of the internship, the difficulties faced, and the strategies adopted to overcome them.
- **Chapter 6 – Conclusion**: provides final considerations regarding the curricular internship and the achievement of its objectives.

2. Overview of the host Institution: Eurotrials, Scientific Consultants

Eurotrials, Scientific Consultants, is a Portuguese, private CRO founded in 1995 in Lisbon by members of academia, medical community and pharmaceutical industry (1). It has a strong local expertise in Europe and Latin America, with offices in Portugal, Spain, Brazil, Argentina, Chile and Mexico (1).

Eurotrials is composed by multidisciplinary project teams including Project Managers, Clinical Research Associates, Study-Start-up and Regulatory Specialists, Data Managers, Statisticians and Medical Writers, that provide the integrated support of a full-service CRO (2). As such, Eurotrials offers a wide range of services in the areas of health and clinical research, including consulting and training services (3). Its various departments have the necessary experience and expertise to participate in all stages of a drug, biological product or medical device development (3).

Eurotrials is organized in different SUs, divided into Business Units (BUs) (Clinical Trials, Real World & Outcomes Research, and Regulatory & Data Sciences BUs) and Support Units (Quality Assurance, Contracts & Proposals, and Teaching & Training). The Eurotrials Portugal's internal organization is described in Figure 1.

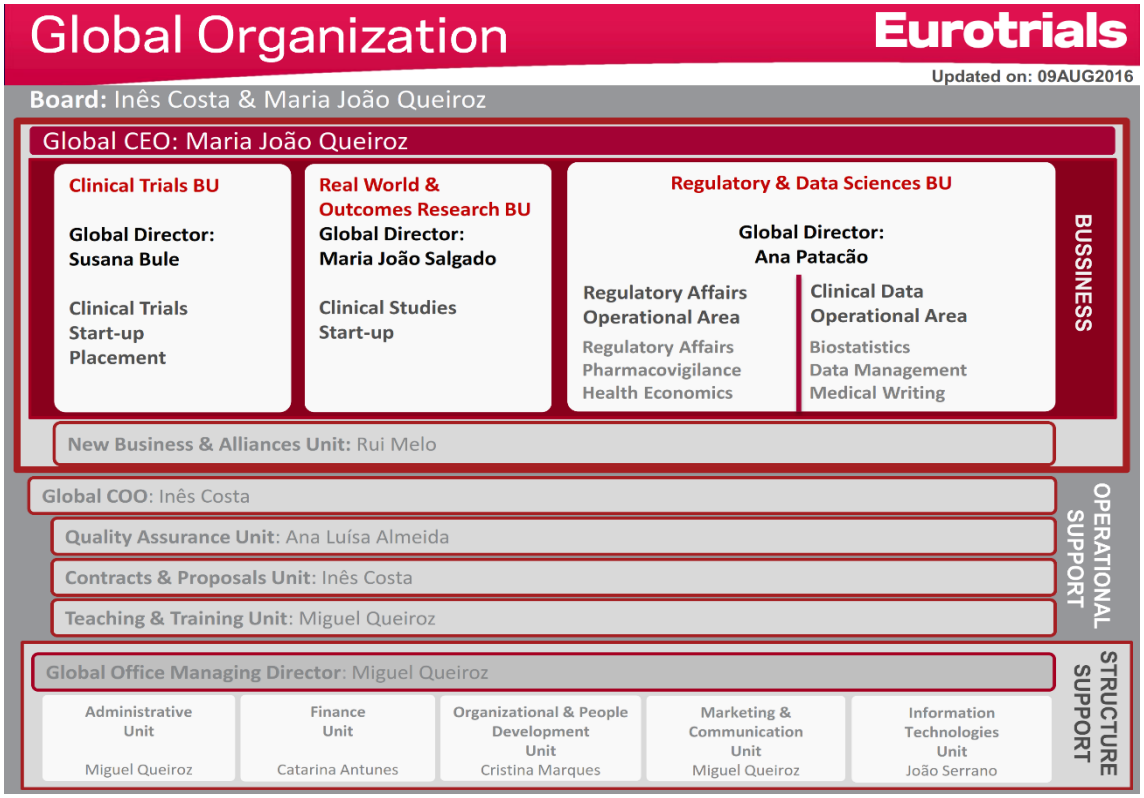

Figure 1 – Eurotrials Portugal's organizational chart (Courtesy of Eurotrials, Scientific Consultants).

2.1 Overview of the Medical Writing Sub-Unit

My internship mainly focused on the Medical Writing SU, which is a part of the Clinical Data Operational Area. This department is responsible for writing different types of technical documents and scoping several therapeutic areas in various geographic regions, namely in European and Latin American regions (4). The Medical Writing SU is a well-experienced, dedicated and organized team offering several medical writing services, such as (4):

- Design and revision of clinical study synopsis (including providing support to define the strategies for the product clinical development);
- Design or revision of clinical study protocols;
- Writing scientific articles, including original papers, reviews, and others;
- Submission of articles to journals, comprising the support in the selection of the most adequate journal and in the peer review process;
- Writing and revision of abstracts and posters to congresses or other events;
- Planning, conducting and reporting of expert Panel/advisory boards;
- Development of clinical study reports (CSR) in accordance with the applicable ICH guidelines and regulatory requirements;
- Variables definition for data collection tools, including case report forms, patient reported outcomes, surveys;
- Writing of informed consent forms and other documentation addressed to the patient;
- Replies to opinions issued by health authorities and ethics committees;
- Literature search for systematic reviews as a background for potential studies, as well as in the scope of health technology assessment studies.

All documents developed by the Medical Writing SU comply with the applicable national and international regulatory requirements, including those from Food and Drug Administration (FDA) and European Medicines Agency (EMA), and universally accepted guidelines, such as the International Conference on Harmonization (ICH)-Good Clinical Practice (GCP), Consolidated Standards of Reporting Trials (CONSORT) and Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) (4).

Currently, the distribution of projects by therapeutic area under the responsibility of Eurotrials' Medical Writing SU is presented in Figure 2.

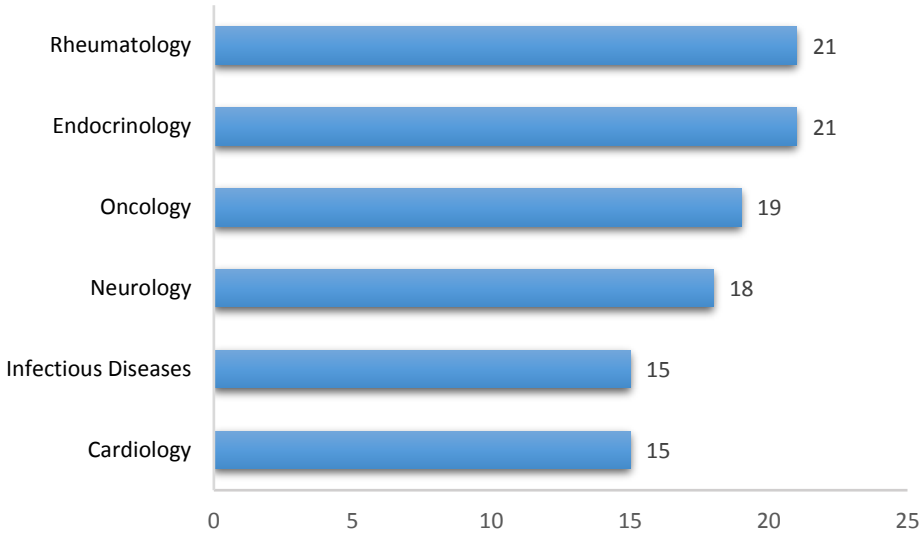

Figure 2 – Number of projects under the responsibility of Eurotrials' Medical Writing Unit by therapeutic area.

3. State-of-the-art

As my internship took place in a CRO, this chapter provides an overview of clinical research studies and of these research organizations, describing their role in clinical research and the evolution of the services outsourced. Additionally, to contextualize the activities performed during my internship, the medical writing landscape is also described, with a special focus on the various types of medical writing, the peer-review process and important guidelines in this field.

3.1 Clinical Research Studies

Clinical studies may be divided into two large groups: interventional (or experimental) and observational studies (5). In interventional studies there is an experimental intervention of the investigators upon the study participants, which generally involves the administration of a given drug, although non-therapeutic interventions may also be applied (such as a new approach at conducting a medical consultation) (6). Observational studies do not involve an experimental intervention, but instead the observation of the relationships between factors and outcomes of interest (5,6). Both types of studies are described in the sections below.

3.1.1 Interventional studies

The most common type of interventional studies are the clinical trials. The ICH GCP E6(R1) defines a clinical trial as "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy". Clinical trials, and more specifically the randomized controlled trials (RCTs), are an essential component of the drug development process. They are characterized by (7,8):

- **Randomization** – ensures that the assignment to treatment groups is arbitrary, balanced, and not influenced by patients' characteristics or physicians' preferences.
- **Blinding** – minimizes the risk of bias when comparing treatments
- **Prospective treatment assignment** – ensures that the outcome is preceded by the intervention, allowing the evaluation of causation.

These features make clinical trials the most reliable tool for establishing a causal relationship between intervention and outcome.

Conventionally, clinical trials have been classified according to four temporal phases (Phases I to IV), which correspond to the phases of development of a drug. Nonetheless, this classification does not represent the most accurate basis for classifying clinical trials (as recognized by ICH), since the same type of trial can occur in different phases of drug development. Alternatively, a classification system based on study objectives is preferable, dividing clinical trials in the following categories(9):

- **Human Pharmacology**: generally conducted during the first phase of a drug development, when a new drug is first administered in humans. They aim to assess a drug's pharmacokinetics and pharmacodynamics, its tolerability, determine its metabolism and drug interactions, and make initial estimates of activity.
- **Therapeutic Exploratory**: these studies aim to explore the therapeutic efficacy of the drug in a selected group of members of a target population. The most adequate dosages to be used in later studies are also determined.
- **Therapeutic Confirmatory**: aimed to demonstrate/confirm the therapeutic efficacy of a drug. They involve larger patient populations and allow the collection of data to confirm the safety and efficacy information collected in previous studies. They are intended to provide an adequate basis for marketing approval.
- **Therapeutic Use**: conducted after drug approval, these trials can be any of the types described above, including studies not deemed necessary for marketing approval, but which are considered important to optimize drug use.

3.1.2 Observational studies

Investigators use observational studies to draw inferences on the effect of an "exposure" or intervention on a group of subjects by directly observing the individuals in their natural setting (10). In these studies, the investigators do not control the intervention they are observing and do not manipulate the assignment of subjects to groups (such as by randomization). Instead, the practice patterns or policy decisions determine which subjects receive the intervention (6).

Observational studies allow investigators to study and identify correlations between variables, such as between patient characteristics or therapies and a given outcome. There are several types of observational study designs, such as:

- **Cross-sectional studies**: these studies consist in the evaluation of a population, represented by the study sample, at a single point in time. The samples are selected in regards to their exposure status, and without considering their outcome status (which is obtained after the enrollment of the patients). They are frequently used to assess the association between a particular exposure and the outcome, but also to determine a given prevalence in the target population (such as the prevalence of a disease) (5).
- **Case-control studies**: in this type of design, the study participants are selected based on their status (i.e., with a given disease [cases] or without [controls]) and the past exposure to risk factors of interest are explored in both groups to determine the ones contributing to the disease development. By quantifying the number of individuals among the cases and controls who were exposed to a given risk factor, it is possible to statistically explore the associations between the exposure and outcome (5,6).
- **Cohort studies**: an example of a cohort study is the prospective follow-up of two groups, one exposed to a given risk factor and the other without the exposure, while recording the occurrence of new cases (incidence) of a disease, for example, during a predefined follow-up period (6).

Data for observational research may have two distinct origins: when data is collected for the specific purpose of answering the study's objectives, it is considered primary data; when data has already been collected for other reasons but is used to answer a new research question, it is considered secondary data (10).

Naturally, observational studies have limitations when comparing with clinical trials, such as the lack of blinding and randomization, which increase confounding. Nonetheless, well-designed observational studies are of utmost importance to understand a particular exposure-outcome association. Whereas the tight controlled environment of clinical trials means that many practical issued encountered in routine clinical practice are not observed (such as patients with concomitant medications and comorbidities), observational studies allow to evaluate the efficacy, safety, tolerability and compliance in a larger and more heterogeneous populations, as well as to identify less common (yet serious) adverse events. Thus, observation studies are an important addition to complementing RCT data with real-world information (7,11).

3.2 Clinical Research Organizations

The ICH-GCP defines a CRO as a "person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions" (12). The sponsor is the entity responsible for the "initiation, management, and/or financing of a clinical trial" (12).

CROs provide clinical trial and other research support services for the pharmaceutical, biotechnology and medical device industries (13). The services performed by these organizations include investigator recruiting and training, study monitoring, data management, statistical analysis, auditing activities, adverse events reporting, medical writing or regulatory services.

In the last 30 years, a significant trend towards extensive outsourcing of drug-development responsibilities to CROs has been observed (14). This tendency is mainly a result of the economic pressure that various major pharmaceutical companies have been facing due to expiring patents and emptier product pipelines, leading to significant job reductions (15). Consequentially, pharmaceutical companies are now developing new products with smaller in-house staffs, which increases their reliance on CROs. By contracting CROs, these companies can acquire specific expertise without the need to hire permanent staff or building the experience in-house, leading to important savings (13). Currently, it is estimated that more than 60% of all clinical studies involve significant outsourcing (14). The sponsors' main reasons to outsource CRO services are shown in Figure 3 (15).

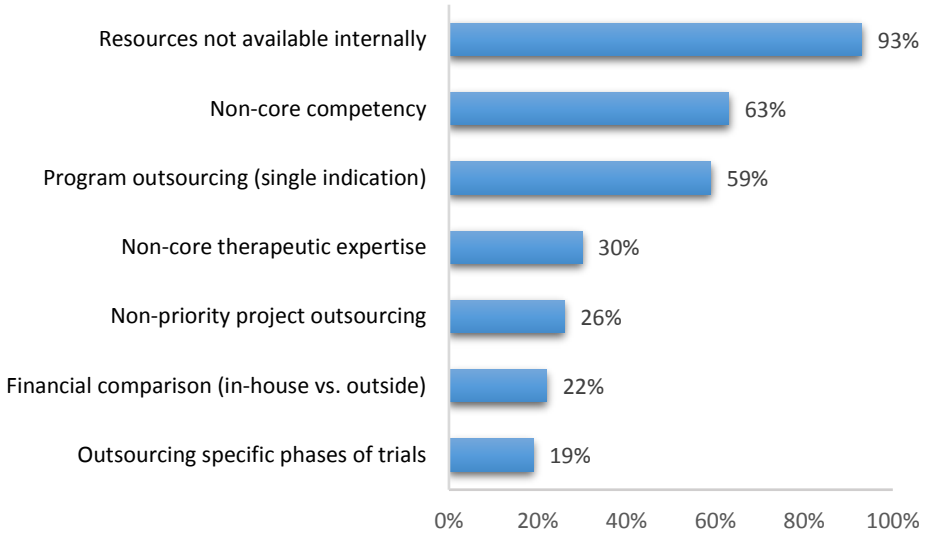

Figure 3 – Sponsors' reasons to outsource CRO services (Adapted from CenterWatch Vendor & Outsourcing Survey, 2005) **(15)**.

Additionally, a wider range of services is being contracted. In 1992, site recruitment and study monitoring were the services most frequently contracted by the sponsors. In the following years, a considerable increase was observed in the use of data management, statistical analysis and medical writing services (14). According to a survey conducted in 2005, the services most commonly outsourced by CROs are depicted in Figure 4 (15):

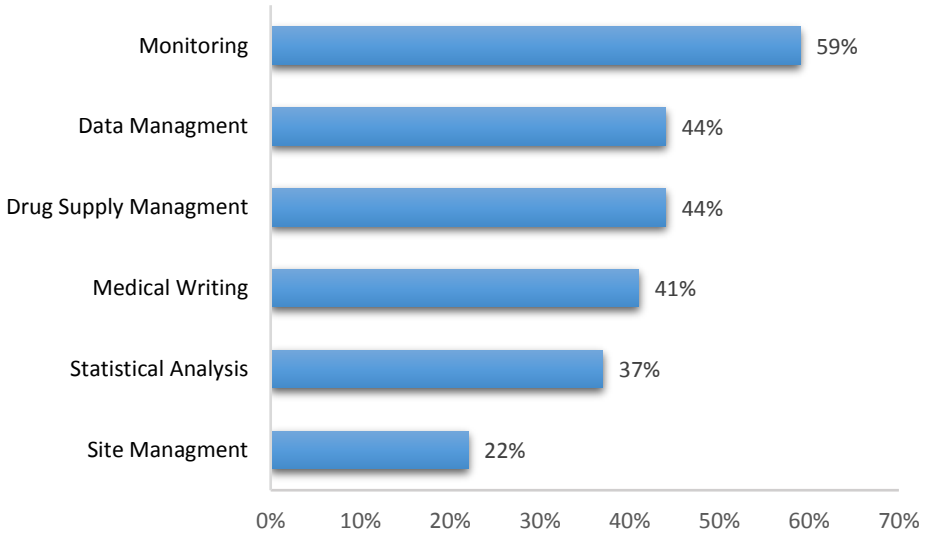

Figure 4 – Most commonly outsourced CRO services (Adapted from CenterWatch Vendor & Outsourcing Survey, 2005) **(15)**.

Nowadays, two distinct client bases drive the market for CROs: large pharmaceutical companies represent 60% of the market, with the majority of the work involving phase III studies, whereas 40% percent of the market is accounted by small biotechnology companies, which mainly outsource phase I and early phase II studies (14).

3.3 Medical Writing Landscape

New knowledge and information is constantly being added to the field of medicine through a continuously increasing number of research studies and growing clinical experience (16). To obtain the most of it, the information produced as a result of these studies and experience should be effectively communicated to various audiences, which may include physicians or other healthcare professionals, patients and consumers, and drug regulators.

Medical writing involves the writing of scientific documents by writers in the field of medicine, known as “medical writers”. Though medical writers are not usually the ones that performed the

actual research, they communicate with the investigators responsible for the generation of the data in research studies in order to present the information in an appropriate manner. Because science benefits from clear and accurate reporting, the importance of medical writing cannot be overlooked: even carefully conducted research generating groundbreaking data can be discredited when poorly presented (16).

In addition to its essential role in converting data from research studies into clear and accurate manuscripts reporting scientific and clinical findings, medical writing is also an important part of the pharmaceutical, biotechonology and medical device industries. This is because specialized knowledge and skills are needed to be able to produce well-structured and clearly presented scientific and regulatory documents required by regulatory authorities throughout the process of development of a drug, biological or medical device.

In the past years, the demand for medical writing has increased. This trend follows the considerable expansion that has been observed in the number of research studies conducted in the biomedical field, which led to an increasing demand for medical writing services in order to convert the data generated in these studies for scientific and medical publications (15).

Additionally, factors related to the pharmaceutical, biotechnological and medical device companies, as well as regulatory authorities' requirements, have also contributed to the increasing demand of medical writing services. These include:

- Various large pharmaceutical and biotechnology companies that used to have large in-house departments of medical writers downsized their teams due to internal restructuring plans, leading to an increase in the outsourcing of medical writing services (15).
- Regulatory authorities require an increasingly amount of documentation during the drug development process (15).
- A higher number of new drugs and medical devices are being developed by pharmaceutical and medical device companies, which means that more regulatory documents need to be developed to submit to the regulatory authorities throughout their process of approval (16).

This increase is reflected in surveys conducted to assess the demand for medical writing, which concluded that medical writing has doubled in size from 2003 to 2008, being the fourth most commonly outsourced service (15). This trend is expected to continue, as long as the amount of

research studies and of documentation required by regulatory authorities for the drug approval process keep on increasing (15).

3.3.1 Types of medical writing

The documents developed by medical writers are varied in their purpose and in the audiences targeted. Thus, medical writing can be divided into various types, such as (16):

- **Publication/Presentation:** Consists in the development of manuscripts such as research articles, review articles and case reports to publish in scientific journals, as well as the development of abstracts, posters and presentations for scientific meetings and conferences.
- **Medical Journalism** – Consists in the development of articles for newspapers and magazines. Whereas the previous type of medical writing is primarily aimed for scientific and medical audiences, these articles mostly target the general public and lay people. As such, they should be written in a simple and non-technical language.
- **Research documents** – Focuses in the development of clinical trial protocols, investigator's brochures, informed consent documents and study reports.
- **Regulatory documents** – Comprises the development of regulatory submission documents, such as Common Technical Documents models (nonclinical and clinical overviews and summaries, safety and efficacy summaries), aggregate safety reports such as periodic safety update reports and annual safety reports, as well as the preparation of prescribing information and patient information leaflets, clinical study reports and subject narratives.
- **Medical Education** – Involves the preparation of educational material in the form of textbooks and e-learning modules targeted to physicians or patients.
- **Medical marketing of healthcare products** – Consists in the development of promotional literature such as product monographs, brochures and handouts for healthcare professionals, and internet content for physicians and patients.

Because the audiences targeted (medical professionals, drug regulators, patients and general public) vary according to the type of medical writing and even within the same type, it is of utmost importance that the language and the level of technical information used is in accordance to the level of understanding of the respective audience. Thus, documents targeted for patients and the

general public must be simple and with no technical jargon, whereas documents for medical professionals and drug regulators can be highly technical, include scientific data and its explanation. Moreover, documents for regulatory submission must comply with specific formats and structures, and their contents must follow regulatory rules and guidelines (such as the ICH-GCP) (16).

3.3.2 Peer-Review Process

The peer review process of manuscripts prior to publication has been used for over 300 years (17). The International Committee of Medical Journal Editors (ICMJE) defines peer review as "the critical assessment of manuscripts submitted to journals by experts who are not part of the editorial staff" (18). Since its introduction, the peer review process has been continuously growing, correlating with the increasing number of manuscripts developed and submitted to journals. In the past, journal editors were rarely selective of the manuscripts reviewed due to the low amount they received. However, as the need for evidence-base medicine grew, the submissions to scientific journals increased to an extent that required a much higher level of selectiveness on what gets published in a journal. The need for peer review was also influenced by the expansion of areas of expertise, which became more specialized and sophisticated. Consequentially, editors could no longer be experts in all areas and began to seek opinions and advice from others (17).

Nowadays, the peer-review process is used in nearly all scientific journals, and it serves three main purposes (17): 1) it helps to identify and select quality articles for publication while rejecting poorly conceived, designed and executed studies. This is accomplished by evaluating an article's scientific merit, validity and methodology, its relevance to the clinical practice, the interest of the topic to the journal's reader, and its overall presentation and understandability; 2) to improve the manuscript whenever possible; 3) to prevent malfeasance within the scientific and clinical community.

3.3.3 Reporting Guidelines and Good Publication Practices

Peer-review publications are among the most important outputs of any research, since they represent the main means of sharing the findings with the research community (19). They are

capable of impacting the medical practice, driving treatment decisions and patients outcomes. Thus, reporting of medical research should be associated with high standards of excellence. Poorly or unclear reporting of a study's methodology and findings impairs its critical appraisal and dissemination. Additionally, inadequate reporting of medical research can lead to unclear and misleading results being used by patients and healthcare providers, which in turn may cause harm to the patients and the use of scarce healthcare resources on ineffective treatments (19).

Thus, recommendations and guidance for the reporting of medical research are provided in reporting guidelines, such as the CONSORT. These guidelines aim at improving the quality of report of studies of various types and at helping readers to more easily understand the design, conduct, analysis and findings of published studies (20). The EQUATOR Network, funded by the National Knowledge Service of the UK National Health Service, assists in the development, dissemination and implementation of reporting guidelines. Following the development of the CONSORT in 1996, several other guidelines have been developed for other types of research studies. Examples of these guidelines are specified below:

- **STROBE (Strengthening of the Reporting of Observational Studies in Epidemiology)** – guidelines for reporting observational studies;
- **PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses** – guidelines for reporting systematic reviews and meta-analyses;
- **STARD (Standards for Reporting of Diagnostic Accuracy Studies)** – guidelines for reporting diagnostic accuracy studies;
- **CARE** – guidelines for reporting case reports;
- **CHEERS (Consolidated Health Economic Evaluation Reporting Standards)** – guidelines for reporting economic evaluations of health interventions.

Empiric studies have demonstrated the value of following these guidelines. One particular study showed that the CONSORT is associated with improvements in the quality of reports of randomized controlled trials (21).

In addition to the reporting guidelines described above, particularly relevant guidelines for medical writers aiming to publish scientific articles are the ICMJE "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" and the "Good Publication Practice (GPP) for Communicating Company-Sponsored Medical Research: GPP3".

The ICMJE guidelines provide recommendations on the best practices and ethical standards in the reporting of research and other material published in medical journals, and the GPP3 provides recommendations for individuals and organizations that contribute to the publication of research results sponsored or supported by pharmaceutical, medical device and biotechnology companies, and aims at helping individuals and organizations to maintain ethical and transparent publication practices and to comply with legal and regulatory requirements.

4. Training Experience

4.1 General Training

At Eurotrials, training is divided into job-specific and project-specific trainings.

My internship began with a training period comprised by a set of required job-specific trainings. Many of these trainings consisted in reading Standard Operating Procedures (SOPs), which are detailed, written instructions to be followed by employees of an organization in order to achieve uniformity when performing a specific function (12). Generally, there are general SOPs, applicable to all employees, and specific SOPs, only applicable for a particular job description.

As a member of the Medical Writing and Biostatistics SUs, I was required to perform the job-specific trainings related to both these departments. On one hand, trainings such as reading the company's Quality Manual, the Code of Business Conduct and Ethic and other applicable SOPs provided a strong basis to understand the basic procedures and the company's organization. On the other, the mandatory trainings related to the activities performed in the Medical Writing and Biostatistics SUs were essential for a better understanding of their scope as well as to become familiarized with some obligatory procedures to be followed during their development. Moreover, job-specific trainings also included reading specific regulatory guidelines, such as ICH's guideline on GCP (E6) and attending the company's annual pharmacovigilance training, mandatory for all Eurotrials' staff. This last training allowed me to understand the pharmacovigilance responsibilities of all collaborators, including how to properly handle relevant safety information, as well as procedures to adequately report safety related information to the pharmacovigilance manager in a timely manner.

Project-specific trainings were related to my participation in specific projects. For example, they could be reading the clinical study protocol, the statistical report, or other related documents, when applicable. They revealed to be important to become familiarized with the projects in which I participated and to comprehend their purpose and objectives.

4.2 On-the-job Training

Throughout my internship at Eurotrials, I was mainly involved in medical writing activities. These included the development of scientific articles of various types, posters to present in scientific congresses, medical information to publish online, and the preparation and submission of manuscripts to scientific journals. My participation in the Biostatistics SU was mostly based on the development of Statistical Reports.

The activities in which I participated are described in the sections below. Due to confidentiality reasons, some studies' results and elements are not specified.

4.2.1 Development of Scientific Posters

At professional conferences, research results are commonly presented in the form of scientific posters (22). A scientific poster is a visual presentation of scientific research presented in a standard form. In conferences, a poster may serve two main purposes: summarize the research conducted in a way that facilitates its communication to conference attendants (for cases in which an oral presentation is also programmed), or to encourage readers to want to learn more (when no oral presentation is planned) (23).

Overall, a poster should be concise and present a clear message. The title is particularly relevant in a scientific poster, as it may be the only part that conference attendees read before approaching the poster. Thus, the title should be short, engaging and comprehensible to a broad audience (23). The poster's layout and format are also critical and should aim to guide the readers from one section to another in a logical fashion, from beginning to end. To that end, the use of arrows or numbering to indicate the logical flow of the poster is advised. Additional general recommendations when developing a poster are to not use a font-size smaller than 24 points and to ensure that the main points are readable at eye level (23).

The text of posters should also conform to the norms of sound scientific reporting: clarity, precision of expression and economy of words (23). The last norm is particularly relevant for posters due to their inherent space limitations, and can be accomplished through the use of figures and tables to summarize the findings and by adapting detailed paragraphs of the original manuscript/abstract into text bullets (22). By following these recommendations, the audience can more readily grasp the key points of the poster.

Activity

During my internship, I was responsible for the development of two posters to be submitted and presented in a pneumology congress. Both posters were to be based on two abstracts previously submitted to the same congress. In addition to following the general recommendations for the development of scientific posters described above, the congress had specific requirements for preparing and submitting scientific posters. Thus, I also had to read and follow the online guidelines available in the congress' website, which specified the minimum font-size, spacing, margins and poster orientation to be used.

The posters were developed using Microsoft PowerPoint and submitted in the congress' online platform.

4.2.2 Clinical Study Reports

The CSR is a critical document in the drug development and regulatory submission process. CSRs are written for regulatory authorities and follow a specific guideline issued by ICH (E3 "Structure and Content of Clinical Study Reports") (24) – which structures the content of CSRs and aims at provide guidance in the development of a report that is complete, free from ambiguity, well organized and easy to review (25).

The ICH-E3 defines a CSR as an "integrated full report of an individual study of any therapeutic, prophylactic or diagnostic agent conducted in patients" (24). A CSR aims to describe the rationale, objectives and results of a study, to include extensive details on demographic data of patients, their course of treatment, and the medical information collected as part of the research, as well as to explain how the study was conducted and the results analyzed (26). The body of a CSR should generally include the following topics (as defined in ICH-E3), although some may be considered as not applicable according to regulatory framework:

1. Title Page;
2. Synopsys;
3. Table of contents;
4. List of abbreviations and definition of terms;
5. Ethics;
6. Investigators and study administrative structure;

7. Introduction;
8. Study objectives;
9. Investigational plan (study design, treatments, variables, quality assurance, statistical methods and changes in study conduct);
10. Study patients;
11. Efficacy evaluation;
12. Safety evaluation;
13. Discussion and overall conclusions;
14. End-of-text tables and figures;
15. Reference list;
16. Appendices.

The appendices (topic number 16) are specific additions of individual regulatory authorities and should be available upon request according to regional regulatory requirements. They may include the study's protocol, sample case report forms, information related to the test drugs/investigational products, technical statistical documentation, related publications, patient data listings, among others.

Activity

Throughout my internship, I participated in the development of CSRs for two studies related to investigational medicinal products. I was responsible for collecting and organizing the documents that comprise the CSR appendices.

As a general rule, the compilation of the CSR appendices should begin in parallel with the development of the CSR. When my participation in the first CSR began, I already had some level of understanding on the process of appendices compilation, due to the training period performed at the start of my internship (which included a specific training on the development of CSRs). Nonetheless, to further understand and identify the documents needed to complete the appendices, I carefully read the ICH-E3 guideline, with a special focus on section 16, which defines the structure and contents of the appendices. According to this guideline, the following documents should be included in the appendices (24):

1. Study information
    1.1 Protocol and protocol amendments

1.2 Sample case report form

1.3 List of Independent Ethics Committees or Institutional Review Boards (plus the name of the committee Chair). Representative written information for patient and sample consent forms

1.4 List and description of investigators and other important participants in the study, including a brief *Curriculum Vitae* or equivalent summaries of training and experience relevant to the performance of the clinical study

1.5 Signatures of principal or coordinating investigator(s)

1.6 Listing of patients receiving test drugs/investigational products from specific batches, when more than one batch is used

1.7 Randomization scheme and codes (patient identification and treatment assigned)

1.8 Audit certificates (if applicable)

1.9 Documentation of statistical methods (includes statistical analysis plans, statistical reports)

1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures (if applicable)

1.11 Publications based on the study

1.12 Important publications referenced in the report

2. <u>Patient Data Listings</u>

2.1 Discontinued patients

2.2 Protocol deviations

2.3 Patients excluded from the efficacy analysis

2.4 Demographic data

2.5 Compliance and/or drug concentration data (if applicable)

2.6 Individual efficacy response data

2.7 Adverse event listings (for each patient)

2.8 Listing of individual laboratory measurements by patient (if applicable)

3. <u>Case Report Forms</u>

3.1 Case Report Forms (CRFs) for deaths, other serious adverse events and withdrawals for AE

3.2 Other CRFs submitted

4. Individual Patient Data Listings (if applicable)

Both projects I was involved started with a kick off meeting with the sponsor. These meetings introduced the projects' background and established the timelines, workflow, deliverables and responsibilities for the preparation of the body text of the CSR. Additionally, topics specifically related to the appendices were also discussed. For example, the documents to be included in the appendices were identified by evaluating which ones were applicable to a particular study. For instance, by assessing whether the study was audited, we were able to evaluate whether audit certificates would be necessary for that study; or, if an abstract or a poster containing study findings had been presented in congresses, we recognized that these publications had to be obtained. Naturally, the type of study also influenced the applicability of some documents: for example, the listing of patients receiving test drugs/investigational products from specific batches and the randomization scheme and codes are not applicable in observational studies. Other important topic of discussion was the definition of whether the CSR (and consequentially the appendices) was to be developed based on the sponsor's or Eurotrials' specific procedures. Regarding the appendices, this decision could impact their formatting and presentation.

The process of compiling the CSR appendices I followed during both projects is described below:

1. First, I had to define a list (similar to the one presented above) stating the documents needed to be included in the appendices. This list was adapted in accordance with the information discussed during the kick-off meeting, by removing the documents considered as not applicable for a particular study.
2. Second, I sent the list compiled in the previous step to the parties that possessed the documents specified. While the sponsor was generally responsible for providing the majority of the necessary documentation, in studies for which the monitoring was performed by Eurotrials, the relevant documents had to be requested to the study' monitors. Because the appendices are to be submitted to regulatory authorities in PDF format, it was important to request all documentation to be sent in this format.
3. Third, I verified the documents received for accuracy. Any inconsistencies found were directed at the sender of the document for clarification.

4. Lastly, I organized the files according to the structure defined in ICH-E3, and named each file in accordance to Sponsor's or Eurotrials' procedures (as applicable).

My participation ended when all applicable documents were obtained and considered accurate, all inconsistencies were adequately clarified, and every file was stored accordingly. The compiled appendices were then sent to the sponsor in PDF format.

The main challenge of these activities were dealing with a great amount of documentation, and ensuring that all documents were obtained, accurate, and correctly organized.

4.2.3 Writing of articles

During my internship period, I was responsible for the development of three distinct types of articles to be submitted in scientific peer-reviewed journals: two original research articles, a systematic review and meta-analysis, and a narrative review. In this section, each type of article I was involved is briefly introduced before describing its process of development.

4.2.3.1 Original Research Articles

Original research articles are categorized as primary literature, which refers to reports of research conducted personally by the authors of the article (27,28). They are the most common type of article published in peer-review journals.

An original research article reports new data based on original research, includes a bibliography review of other literature and is supported by statistical analyses (29). In these articles, researchers present their hypothesis or research question and the rationale for the study, detail the research methods, present, interpret and discuss the possible implications of the results, and draw conclusions based on the findings.

These types of articles generally consist of a title, abstract, keywords, introduction, material & methods, results, discussion and references. This basic structure is known as the IMRAD (Introduction, Methods, Results and Discussion) structure (29).

Observational study

This project consisted in the development of an original research article related to an observational study that was conducted to assess the efficacy and safety of an antiepileptic drug. The article was developed based on literature provided by the sponsor, comprising observational studies and clinical trials that also evaluated the safety and efficacy of the same antiepileptic (to establish comparisons with the study findings), and on a statistical report previously developed by the Biostatistics department, describing the study's methodology and results.

This was the first article developed during my internship. I read and followed the STROBE guideline, applicable for observational studies, which revealed extremely helpful to recognize how to structure the article and to identify the necessary information to report in each section.

Delphi Panel

The Delphi method was originally developed by Dalkey and Helmer in the 1950s. It is a commonly used and accepted method of obtaining real world data from a panel of participants regarding their domain of expertise. In this method, consensus regarding a particular topic being examined is sought from the participants (selected experts). To that end, several rounds of questionnaires are sent to the experts, and the anonymous responses are combined and shared with the group following each round, to provide feedback and to further the discussion. In the subsequent rounds, the experts are able to adjust their answers. Generally, the experts modify their responses as rounds are completed, based on the information specified by other experts participating in the panel. The questionnaire rounds may be repeated as many times necessary to achieve a general consensus (30,31).

The main advantages of this method include the subject anonymity, which may reduce the bias of response due to the effect of dominant individuals and because the panelists do not need to worry about repercussions of their opinions, and an ease to obtain information from experts of distant geographic regions by using electronic communication such as e-mail to exchange information.

Activity

My participation in this project consisted in the development of an original research article aimed at describing a Delphi panel conducted to characterize the clinical practice of a hematological

disease in Portugal. The first step of this project consisted of a meeting with the Biostatistics department, which had developed the study's statistical report. During the meeting, the rationale, objectives and methodology of the Delphi panel were explained, and the results obtained were specified. After becoming familiarized with the project, I attended a meeting with the sponsor, in which aspects such as the scope of the manuscript and the most suitable journal for submission were discussed, and relevant literature to develop the manuscript and to compare the results obtained during the panel was specified and made available.

A particular challenge during this project was related to my lack of experience in Delphi panels and the fact that no specific guideline for the reporting of these panels was available. Thus, before beginning to write the manuscript, I read various articles of studies using the Delphi methodology in order to become familiarized with their reporting. Additionally, I had to acquire knowledge on the hematological disease of this study and the treatments used in its management. To that end, guidelines from entities such as the National Comprehensive Cancer Network and the National Institute for Health and Care Excellence regarding the management of this hematological disease were essential.

The manuscript was developed based on self-searched literature, the statistical report, and an observational study conducted in various European countries that also evaluated the management of this hematological disease.

4.2.3.2 Review Articles

Review articles are considered as secondary literature, which consists of publications that rely on primary sources for data (such as original articles) (27,28). Their main purpose is to summarize and synthesize knowledge in a specific area and, as such, it is not required that the authors have performed the research themselves.

Review articles provide a comprehensive summary of the research conducted on a certain topic, and offer a critical perspective on the state of the field and where it is heading. They are usually widely read (for example, by researchers looking for a full introduction to a specific field) and highly cited.

Systematic review and meta-analysis

Globally, a substantial expansion of research output, including peer-reviewed publications and unpublished data has occurred. This has made it difficult for clinicians and researchers to keep up to date with the best research evidence and to identify the research already performed in a specific area (32). Moreover, following a literature search on a specific clinical question, a considerable number of articles is usually retrieved, which may have conflicting results and variable quality (33). Thus, healthcare decisions should not be based solely on the results reported by one or two studies, but rather take into consideration the entirety of research information available for that specific problematic (33).

The points described in the previous paragraph help to understand the importance of systematic reviews and meta-analysis and their role in the medical context. They allow to summarize the outcomes of various studies and, therefore, are an exceptionally effective method to determine whether an intervention is efficacious or not (32). In fact, systematic reviews of RTCs are considered the highest level of evidence regarding research designs to evaluate the effectiveness of interventions (34).

A systematic review aims to answer a specific research question through the collection and summarization of all empirical evidence that complies with pre-specified eligibility criteria (35). It is most useful when there is a substantive research question; there are a considerable number of empirical studies published; and there is uncertainty regarding the results (36). Systematic reviews can be of interventions, such as RCTs, or observational studies (case controls, cohorts). The use of observational studies to conduct systematic reviews has been common in areas such as sociology and psychology, as the great majority of studies performed in these disciplines are of observational nature (36).

To be useful to other researchers and clinicians, systematic reviews should respect various aspects. These include:

- Clearly specified objectives and eligibility criteria defined *à priori*;
- Well explained and reproducible methodology;
- A literature search that aims to identify all relevant studies;
- An assessment of the validity of the included studies' findings (risk of bias);
- Clearly synthesized characteristics and findings of the included studies.

A meta-analysis is the use of statistical methods to summarize the results of the studies selected during the systematic review. The rational of the meta-analytic process is that the overall sample size is increased by pooling the results of various individual studies, which in turn increases the statistical power of the analysis and the precision of the treatment effects' estimates (33). Moreover, meta-analyses may have sufficient power to investigate clinically important subgroups (37).

The meta-analysis process can be divided into two stages. In the first stage, a measure of effect size and the respective 95% Confidence Interval (CI) are calculated for each individual study considered for the analysis. Whereas traditional hypothesis testing give information regarding statistical significance (i.e., were there differences in the intervention and control groups) but not necessarily clinical significance (i.e., was the difference observe clinically meaningful or large), effect sizes measure the strength of the relationship between two variables, which allows to evaluate the magnitude of the intervention effect (small, medium, or large) (32). The type of outcome and intervention examined and the data available from published trials will often define the type of effect size calculated. Commonly used effect sizes include odds ratios, relative risks, and weighted/standardized mean differences (32). In the second stage, the overall effect of the intervention is calculated using a weighted average of the effect size of the individual studies. A key point in a meta-analysis is that greater weights are given to the results of studies providing more information, as they are more likely to be closer to the "true effect" we are trying to estimate. Generally, the weights are calculated as the inverse of the variance (the standard error squared) of the treatment effect, which relates to the sample size and the precision of the results (33).

The process of conducting a systematic review and meta-analysis can be divided into several steps (32,33):

First step - Formulating the research question, forming hypotheses, and developing a review title. The formula '*Intervention* for *population* with *condition*' is usually used to define a descriptive and short title.

Second step - Definition of inclusion and exclusion criteria. The acronym PICO (standing for Population, Intervention, Comparison and Outcomes), proposed by Cochrane, is useful to define all major components before the start of the review. Additionally, defining the types of studies to be included and excluded (i.e., only RCTs or only observational studies, only published versions or published and unpublished versions), the minimum number of participants in each group (intervention and control), and language restrictions should also be defined *a priori*.

Third step - Literature search. It is essential to define a set of key search terms related to each component of PICO to identify all studies relevant to the question defined. A key aspect in this step is to balance sensitivity (i.e., retrieving a high proportion of relevant studies) with specificity (retrieving a low proportion of irrelevant studies). The search usually involves various relevant electronic databases (Medline, EMBASE), but can also comprise checking the references of selected articles, hand-searching key journals, and personal communications with experts or researchers in the field.

Fourth step – Selection of the studies retrieved in the literature search, usually based on their title, abstract and keywords. Following this selection, the full-texts of the studies meeting the inclusion criteria are obtained and reviewed. It's important that this process is performed by two or more independent reviewers so that the results can be discussed and the inter-rater reliability assessed. Moreover, the reasons for inclusion and exclusion of the studies reviewed should be recorded. Contacts with the study authors are often required to obtain data not specified in the article but that is needed for the data pooling, such as means or standard deviations.

Fifth step - Data extraction. It's advised to develop and use a simple data extraction form to summarize the information extracted from each study selected. Examples of information generally collected include the authors, publication year, number of participants, study design, outcomes, and the status 'included' or 'excluded'. Similarly to the selection of studies, this process should be carried out by two or more independent reviewers to validate the data inserted and avoid data entry errors.

Sixth step - Assessment of the studies quality. Various tools are available to perform this assessment, and the choice will depend on the type of study included in the review. Most of these tools are checklists, in which specific questions related to the study quality are specified. For randomized trials, the most commonly used tool is the Cochrane Collaboration's Risk of Bias tool (38), and entities such as the CONSORT Statement provide various others.

Seventh step - Analyzing and interpreting the results. Several meta-analytic software allow the estimation of effect sizes for meta-analyses, such as the Review Manager (RevMan) by the Cochrane Collaboration. The effect sizes are usually presented together with a 95% CI, both in quantitative form and in a graphical representation (forest plots).

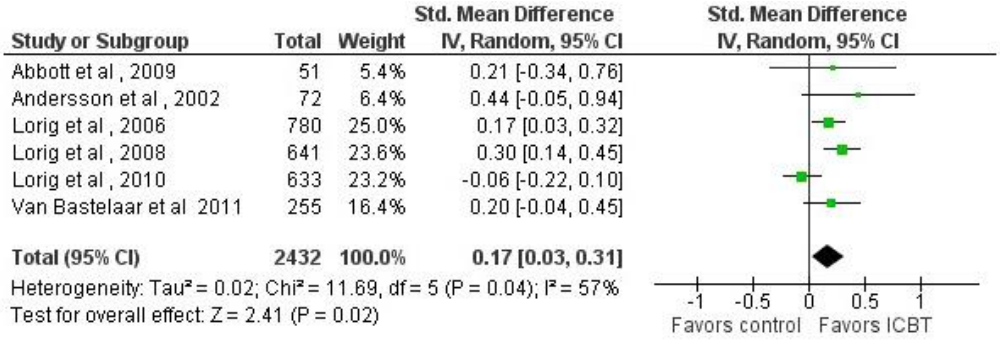

Figure 5 – Example of a forest plot **(39)**

In the forest plot example shown in Figure 5, each horizontal green squared shape represents one study, with the middle representing the effect size and the extremities the ends of the CI. The center line of the graph represents the zero mark. In this example, the left side (<0) is the side favoring the control, whereas the right side (>0) favors the intervention. The single black diamond in the bottom of the graph represents the combined effect size of all individual studies pooled together. Because the entirety of the diamond is at the right side of the graph, the intervention is favored over the control. This is confirmed by the statistically significant value of the test for overall effect (p=0.02). Considering to what extent the results are consistent is also important. Generally, a poor overlap of the CIs (horizontal lines in the figure) for the results of each included study indicates the presence of statistical heterogeneity. To formally determine if heterogeneity is present, the software commonly calculate and present heterogeneity measures. In the example shown in Figure 5, the value for the chi-square and the corresponding p-value, as well as the I^2 index, are presented. The chi-square assesses whether the differences observed in the results are due to chance alone, and the I^2 allows to quantify the heterogeneity. This index may be interpreted according to the intervals defined below (38):

- 0-40% - non-relevant heterogeneity;
- 30-60% - moderate heterogeneity;
- 50-90% - substantial heterogeneity;
- 75-100% - considerable heterogeneity.

Non-statistically significant values for heterogeneity are preferred. In this example, however, the value for chi-squared (11.69) is statistically significant (p=0.04). Moreover, the I^2 index indicates that we are in the presence of moderate to substantial heterogeneity. Nonetheless, heterogeneous studies may still be pooled together, though the results should be interpreted with caution and the reasons for heterogeneity explored (38).

Two models can be used during a meta-analysis: the fixed-effects and the random-effects models. In a fixed-effect analysis, it is assumed that the true effect size is the same across all studies, and the summary effect is the estimate of this common size. Thus, it is assumed that the true effect size for all studies is identical and sampling error (error in estimating the effect size) is the only reason behind the variation in effect sizes between the studies. In a random-effects analysis, it is assumed that the true effect size varies across studies and the studies in the analysis represent a random sample of effect sizes that could have been observed. The summary effect is the estimate of the mean of these effects (38).

Both methods will provide identical results when there is no heterogeneity among the studies. When heterogeneity is present, a random-effects meta-analysis weights the studies more equally than a fixed-effect analysis and the CIs for the average intervention effect will be wider, and corresponding claims of statistical significance will be more conservative (38).

Sensitivity analyses are also an important component of a meta-analysis, as they allow to explore the influence of biased studies and of decisions made throughout the systematic review and analysis processes. Usually, they consist in repeating the meta-analysis by excluding studies considered as having a high-risk of bias (according to the previous step), which allows to evaluate whether the overall results and conclusions are influenced by their inclusion. Moreover, consistency between the results of the primary analysis and the sensitivity-analysis strengthen the conclusions and credibility of the findings (40).

Eight step - Writing process to summarize the findings and provide recommendations for medical practitioners (which interventions are efficacious, in which populations) and for the areas requiring further research, and consequently the study publication and the dissemination of the findings.

Activity

During my internship, I participated in a systematic review and meta-analysis to evaluate personality traits and psychopathology in adults with fibromyalgia. This project was the core of my internship and, consequently, the task in which I spent more hours working on. It combined biostatistics and medical writing, as I was involved in the statistical analysis of the results and in the writing of the manuscript.

The evaluation of personality traits and psychopathology can be made through self-assessment questionnaires, in which individuals answer specific questions regarding personality with a numeric value. Generally, these questionnaires are composed by various scales, each one evaluating a distinct personality trait. In this questionnaire, if the combined result of the values specified by the participants for the questions relating to a given personality trait are above a specific numeric cut-off, the result is considered clinical significant. The main objective of this project was to identify the scales clinically elevated in the fibromyalgia population. For this systematic review and meta-analysis, two different versions of a particular questionnaire were chosen as the intervention.

According to the acronym PICO, the population of this study are adult patients with fibromyalgia, the intervention is the self-assessment questionnaire, no control group was considered, and the outcome were the questionnaire results.

At the time I was assigned to this project, the literature review to identify relevant articles had already been performed (third step). Thus, my participation began with the selection of the studies based on the full-text versions and the inclusion/exclusion criteria previously defined. To that end, I assessed the articles' full texts to evaluate whether the study population included fibromyalgia adult patients, the self-assessment questionnaire was applied (either version), and the data needed for the analysis was specified in the results section.

Following this step, I developed a data extraction form that aimed at collecting the most relevant information from the articles complying with the eligibility criteria. This information included the primary author, year of publication, number of patients with fibromyalgia, study population characteristics, fibromyalgia diagnostic criteria, version of the questionnaire, and outcomes. As recommended, the sponsor simultaneously and independently evaluated the full text versions for eligibility, created a data extraction form and collected the data accordingly. A meeting with the sponsor was then scheduled, in which the data extracted by both reviewers were compared and the rational for the inclusion or exclusion of the articles was discussed.

The next step was the quality assessment of the studies, which started with the definition of the criteria to be used to identify studies with a high risk of bias. As this was not a systematic review of clinical trials, for which specific criteria to assess risk of bias exists (such as the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (38), I had to search for risk of bias tools related to systematic reviews of studies reporting self-assessment questionnaire results. Nevertheless, no tool revealed adequate for our study. Thus, in the absence of an established and appropriate risk of bias tool, we had to define a set of criteria that, in our opinion, were relevant

indicators of each study's risk of bias. Then, using the data extraction form, I assessed whether each study complied with all the criteria defined. Studies not respecting one or more criteria were defined has having a high risk of bias.

The next step was defining the statistical method that would be used to perform the analysis of the data, which was discussed during a meeting with a Eurotrials' Biostatistics consultant. The effect sizes were the means of the results for each scale, reported in the studies included in the meta-analysis. The initial idea was to conduct the analysis using a software that allows to perform meta-analysis of the data entered (RevMan). Nonetheless, while exploring the software, I noticed that it required the existence of a control group in order to perform the analysis. This revealed to be one of major obstacles encountered during my participation in this activity: because our aim was to pool the mean results reported in the individual studies solely for the fibromyalgia group, we had to decide on an alternative statistical method. Thus, in a new meeting, the Biostatistics consultant defined a set of formulas that would allow to perform the analysis and obtain the desired results without the need for a control group. These formulas aimed at obtaining an adjusted weighted mean, the respective standard error and a 95% confidence interval for each scale of the questionnaire, and are described below:

$$\bar{\boldsymbol{X}} = \frac{\sum \boldsymbol{\omega_i}\ \bar{\boldsymbol{X}}_{\boldsymbol{i}}}{\sum \boldsymbol{\omega_i}}, \tag{1}$$

where $\bar{X}$ is the adjusted weighted mean, ω_i is the weight of the studies (calculated as the inverse of the variance) and $\bar{X}_i$ is the adjusted mean of the scores of each scale,

$$\boldsymbol{EP}_{\bar{\boldsymbol{X}}} = \sqrt{\frac{\mathbf{1}}{\sum \boldsymbol{\omega_i}}}, \tag{2}$$

where $EP_{\bar{X}}$ is the standard error of the adjusted weighted mean,

$$\boldsymbol{CI}\ (\mathbf{95}\%) = (\bar{\boldsymbol{X}}\ \pm \mathbf{1.96}\ \boldsymbol{EP}_{\bar{\boldsymbol{X}}}), \tag{3}$$

where CI is the confidence interval.

Additionally, we used the Chi-squared test to evaluate the heterogeneity of the scales across the studies. The following equation was used:

$$\boldsymbol{Q} = \sum \boldsymbol{\omega_i}\ (\bar{\boldsymbol{X}}_{\boldsymbol{i}} - \bar{\boldsymbol{X}})^{\mathbf{2}}, \tag{4}$$

where k is the number of studies.

This value was compared to the tabulated values of the χ^2 distribution to assess its statistical significance (values higher than the tabulated ones for a given significance level and degrees of freedom are considered statistically significant) and, consequently, to infer about the presence of heterogeneity. The degrees of freedom are the number of studies included minus one.

Moreover, the I^2 index was also calculated, in order to quantify the heterogeneity of each scale across studies:

$$\boldsymbol{I^2 = \frac{Q-(k-1)}{Q} \times 100\%}, \quad (5)$$

Another obstacle was the fact that the studies selected for the analysis used two different versions of the questionnaire. Although both versions measure essentially the same (personality traits and psychopathology), the values obtained for each scale in one version are a specific and constant value above the other, due to the use of different normative samples. Consequentially, the cut-offs to define clinical significance also differ the same constant value. Thus, we had to make an initial correction to the values extracted from the articles so that both versions could be combined. This was accomplished by subtracting the specific cut-off of each version to the respective results reported, which allowed to obtain adjusted values representing the distance to the cut-off (positive values were considered clinical significant).

All these calculations were performed using a spreadsheet program (excel). Throughout this step, the contact with the biostatics department was crucial to clarify doubts about the formulas and to successfully carry out the analysis.

The next step was to carry out the sensitivity analyses. This consisted in repeating the analysis while excluding all studies identified as having a high risk of bias. Moreover, we also performed an additional sensitivity analysis that only included the studies using the most recent version of the questionnaire, to evaluate whether the results were robust to the type of version used.

After a new meeting with the sponsor, an additional analysis involving comparisons between the results obtained by fibromyalgia patients and healthy volunteers in each scale was planned. In this case, the effect sizes were the mean differences between both groups, and, due to the existence of a control group (healthy volunteers), I was able to carry out the analysis in RevMan. Additionally, some scales presented significant levels of heterogeneity, which warranted the use of random-effects models.

With the main results obtained, I began to write the first draft of the manuscript. Because systematic reviews and meta-analysis articles are organized differently comparing to standard journal articles, I had to become familiarized with their particular structure. To that end, I searched for guidelines and checklists that define the structure and the most important information to be reported, as well as for systematic reviews and meta-analysis articles published in the target journal. We used the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement from PRISMA, which consists in a 27-item checklist aimed at facilitating the transparent reporting of systematic reviews (41).

Narrative Review

A narrative review is a type of article aimed at objectively report the current knowledge on a specific topic and to base this summary on previously published literature. It provides a comprehensive overview and helps to place that information into perspective (42).

Given that numerous sources of information are retrieved and their findings synthesized, these type of articles are extremely valuable for clinicians and other researchers. For clinicians, narrative reviews allow to economize time when reviewing or searching for information (e.g., patient care) by summarizing great amounts of information into a single article (42). For researchers, they allow to identify, justify and refine hypotheses and to avoid pitfalls recognized in previous research.

Both narrative and systematic reviews are subject to systematic and random errors. The main feature distinguishing narrative reviews from systematic reviews is the extent to which scientific review methods have been used to minimize error and bias. The key differences between these two types of review articles are summarized in Table 1 (43,44).

Table 1 – Key differences between narrative and systematic reviews.

Features	Narrative Reviews	Systematic Reviews
Question	Broad	Specific
Search strategy	Not usually specified	Comprehensive search conducted in a systematic way
Study selection	Process for selecting studies not usually specified (potentially biased)	Comprehensive sources; eligibility criteria specified
Study quality evaluation	Variable	Rigorous critical evaluation; methods to assess risk of bias specified
Synthesis	Often qualitative	Quantitative (usually involving a meta-analysis)

Reviews complying with the methods outlined in the right column are more likely to be systematic and to provide unbiased conclusions, whereas reviews using the review methods described in the middle column have conclusion that are less likely to be based on an unbiased summary of all relevant evidence.

In cases where a considerable amount of quality data is available, a quantitative synthesis using meta-analysis in the context of systematic reviews is much more valuable than a qualitative synthesis in a narrative review.

Additionally, because of more rigorous review methods, systematic reviews are more likely to detect methodological limitations of primary studies included and of potential sources of bias. Thus, they generally produce more conservative conclusions in comparison to narrative reviews. Notably, systematic reviews often conclude that there is a lack of quality information in the literature on a specific topic. Though such conclusion is generally not the one intended, it is valuable to highlight the areas where further research is needed (37).

Nonetheless, narrative reviews are still of great value when the main objective is to obtain a broad perspective on a specific topic, rather than providing quantitative answers to specific clinical questions (43). Because of the limitations described above, authors should make efforts to minimize bias as much as possible by using proper writing and research techniques, and a high level of objectivity, which leads to improved utility and credibility of the publication (42).

Activity

The main objective of this project was to estimate the potentially preventable cases of pneumococcal pneumonia with the 13-valent pneumococcal conjugate vaccine in the Portuguese population aged over 65 years. This estimative was obtained based on data identified during a literature search performed by the sponsor and the main findings were presented at a pneumology congress in the form of an abstract and a poster.

The article was planned to be a narrative review focusing on the current state of pneumococcal pneumonia hospitalizations and antipneumococcal vaccination recommendations in Portugal, in which the findings summarized in the previously developed abstract and poster were described and discussed to a greater detailed.

4.2.4 Editorial Process

The aim of most research projects is to publish them in a peer-reviewed journal. Though peer review can be a lengthy and exhausting process, it's the publication of the manuscript that effectively validates the research developed and allows it to be shared with other researchers and clinicians in the field (45). Throughout my internship, I was involved in the editorial process of several manuscripts. My participation included the selection of the most suitable journal for a given manuscript, formatting the manuscripts according to the selected journal's requirements, and submitting the manuscripts in the journal's online platforms. The only stage in which I did not participate was the peer-review process. The steps of the editorial process that I followed for each manuscript are described in the sections below.

4.2.4.1 Journal Selection

One key step in the publication process is to select the most suitable journal to submit the manuscript (45). Choosing the right journal is essential to reach the desired target audience, for which the manuscript's findings have the most interest.

Thought I was responsible for selecting the most suitable journal for various manuscripts, the steps I followed were generally the same. First, I began by identifying a set of potential journals. This was accomplished by searching for journals that aimed to publish in the same research field as the

research conducted. For example, if the manuscript reported a study performed to assess the efficacy of an antiepileptic in the prevention of seizures in epileptic patients, I would consider journals publishing in the neurology area. Another valuable method to identify potential journals was to check the references of the manuscript to be submitted, as they were likely to be published in journals of the same research area.

Following the identification of potential journals, I evaluated the ones selected according to the following factors:

- **Journals' aims and scope** – This information can be easily accessed in the journal's homepage and allowed me to evaluate whether the research performed was a good match for a particular journal, as it specifies the journal's target audience and research field. For instance, the Epilepsy Journal states that its main aim is "to provide the knowledge on epilepsy globally to the readers, promote and encourage research on epilepsy and also provide the latest updates on the diagnosis, treatment and management of people with epilepsy". Thus, the above mentioned manuscript reporting the research on the efficacy of an antiepileptic would be a good fit for this journal. Complementarily, searching for articles similar in terms of scope to the one intended for submission also revealed to be useful to assess whether a particular journal was a good match. The identification of similar previously published papers is often a clear indicator that the research topic is of interest to the audience of a particular journal, increasing the chances for review (45).
- **Type of articles accepted for publication** – Some journals do not accept particular types of articles (such as case reports). Submission to a journal that does not accept the type of article chosen to report the research conducted is often immediately rejected (45). Thus, it was of utmost importance to read the "Information for Authors" section of the journal, in which the types of articles accepted for publication are generally specified.
- **Word count restriction** – Journals frequently define word count limits which vary according to the article type and across different journals. A common word count restriction is the 4000 words limit defined for original research papers. As such, I had to ensure that the manuscript to be submitted did not exceed the word count limit allowed by the journals selected for its specific article type. This information is also specified in the "Information for Authors" section.

After confirming that a manuscript was a good fit for the journals and that it complied with the journal's requirements in terms of article types accepted and respective word count limits, I

evaluated and compared the set of journals selected with regards to various factors that help to identify the most adequate one. These are called the journal metrics (46), which can divided into three: speed, reach and impact.

The speed relates to the journal's performance in terms of average time to review and publish (46). This metric can be assessed by evaluating the title page of articles previously published in a particular journal, which usually state the date of submission, date of acceptance and date of publication. By evaluating the time elapsed between the submission and publication dates, I was able to infer about the speed of a journal.

The reach relates to the geographic location of corresponding authors and journal usage (46), and is based on the number of downloads and number of primary authors at the country level. This metric assumes particular relevance when the research conducted is mainly of interest for the country in which it was performed (for example, the evaluation of potentially preventable cases of pneumococcal pneumonia in Portuguese hospitals is particularly relevant for Portuguese healthcare professionals and patients).

The impact is evaluated through the journal's impact factor (IF). Although the validity of the IF as a metric for journal quality is controversial, it remains the default method to determine the reputation of a journal (45). The IF is based on the number of times the articles of a journal are cited in a given year, and can be calculated according to the following formula (47):

$$IF = \frac{X}{Y}$$

Where X is the number of times the journal articles were cited in a given year and Y is the number of citable articles published by the journal in that same year. The IF is frequently stated in the journal's homepage.

Despite its widespread use, the IF should be interpreted with caution as it may greatly vary depending on the research area. Articles published in an area where little research has been conducted will be less cited and lead to lower IFs in comparison to articles published in extensively researched areas.

In addition to the journal metrics described above, I also considered factors such as the journal's acceptance rate and visibility, which may also influence the choice of the journal (48). A low acceptance rate indicates that only the best and most relevant articles are published, whereas a

high visibility journal is one indexed in multiple computerized databases (such as Medline, Scielo, EMBASE) and allows articles in the journal to be retrieved by searching these databases.

4.2.4.2 Preparing the manuscript

After identifying the most suitable journal, a manuscript must be formatted according to the target journal's requirements and sent to one journal at a time only. Submitting the same work to more than one journal simultaneously is a serious ethical violation (48).

To prepare the manuscript for submission, I read and followed the submission guidelines which are commonly available on the journal's website, in the 'Information for authors' section. These should be carefully followed to ensure that the manuscript is formatted in accordance to the journal's requirements. The guidelines usually specify the file formats for the manuscript and figures, the manuscript (font-size, spacing, and margins) and reference styles to be adopted, and the main sections to be considered. Though variable depending on the journal and article type, the body of the manuscript is usually divided into Introduction, Methods, Results, Discussion and Conclusion, known as the "IMRAD" structure.

4.2.4.3 Submitting the manuscript

To carry out the process of submission I also referred to the journals' submission guidelines. These specify the documents needed for submission (such as the cover letter, the manuscript, the tables and figures) and the order in which they should be uploaded in the submission platform. The cover letter is a short document (generally containing one or two pages) that accompanies the manuscript in its submission. Ultimately, the cover letter aims at influencing the editor's decision of sending the manuscript for peer review. To that end, it should introduce the research conducted, its rationale and importance, highlight the most important findings reported, and specify the reasons justifying why the manuscript is a good fit for the journal and why the findings are of interest to the readership. Depending on the journal, the suggestion of peer reviewers (experts in the topic area of the manuscript and not recent collaborators or from the same institution as the authors) may also be requested.

4.2.4.4 Peer review

After submission, the manuscript is read by an editor to evaluate its adequacy for the journal. Three main points are usually considered: 1) the manuscript falls within the scope of the journal; 2) the manuscript follows editorial policy and general guidelines; 3) the content of the manuscript does not present an unacceptable level of overlap with manuscripts already in press. When one or more of the previous conditions are not verified, the manuscript may be rejected without additional review. If all conditions are verified, the manuscript is sent to additional reviewers (17).

Two main types of blinding may be used during the peer review process: the single-blinded review and the double-blinded review. In the single-blinded review, the authors are unaware of the reviewers' identities but the reviewers know who wrote the manuscript. This type of review has been subject of criticism and debate due to the potential bias associated with it. In the double-blind review, the authors' identity is also masked during the review process (17).

Following revision, the reviewers return their recommendations and reports to the editor, who assesses them collectively and decides whether to reject the manuscript, to withhold judgment pending major or minor revisions, to accept it pending satisfactorily completed revisions, or to accept it as written (17).

When applicable, the minor or major revisions are specified to the authors via e-mail. The manuscript should then be modified accordingly and a revised version should be re-submitted. This version will repeat all or some of the stages described above. Once a manuscript has been revised satisfactorily, it will be accepted and prepared for publication (17).

This was the only step of the editorial process in which I did not participate during my internship.

4.2.5 Information to publish online

In addition to the information presented in scientific journals and congresses, a considerable amount of information is also generated as "web content" for medical professionals and the general public.

During my internship, I also had the opportunity to participate in the type of medical writing called "Medical Education" (See Section 3.2.1). I was responsible for the development of a summary of the pneumococcal vaccination recommendations in Portugal, which was intended to be published online and was mainly targeted for healthcare professionals and patients.

The main challenge during the writing of this summary was the fact that, while all projects I had previously developed (research articles and scientific posters) were targeted for specialized audiences with a high level of understanding, this information was also meant to be read by patients. As such, I had to adapt the language used accordingly, by making efforts to use simple language only and to avoid technical terms.

4.2.6 Biostatistics Activities

My participation in the Biostatistics SU was brief and mainly based on the development of statistical reports. A statistical report is a document describing a study's methodology, statistical results and statistical conclusions. Generally, they are divided into the following sections:

- Introduction
- Study objectives
- Investigational plan
    - Study design
    - Selection of study population
    - Treatments
    - Efficacy and safety endpoints
- Statistical methods planned in the protocol and determination of sample size.
- Study patients
- Demographic and other baseline characteristics
- Efficacy results
- Safety results
- Statistical conclusions
- References

Throughout my internship, I participated in the development of statistical reports for three studies. My role consisted in adapting the relevant information presented in the studies' statistical analysis plans and protocols, and to describe its results and conclusions. A statistical analysis plan is a document containing a more technical and detailed information about the main features of the analysis described in a study's protocol, and includes detailed procedures for the execution of the statistical analysis of the primary and secondary variables and other data.

5. Discussion

The activities in which I participated during my internship are listed in Table 2.

Table 2 – Activities performed during the internship.

Activity	Number of projects
Medical Writing	
Scientific Articles	4
Scientific Posters	2
Preparation and submission of manuscripts to scientific journals.	3
Clinical Study Reports (compilation of appendices)	2
Information to publish online	1
Biostatistics	
Statistical Reports	3
Meta-analysis	1

As it is clear by observing the table above, the medical writing activities were the main focus of my curricular internship. Over the course of this 9 month period, I participated in various activities often developed by medical writers: development of scientific articles, preparing and submitting manuscripts to scientific journals, development of posters to be presented in scientific congresses, clinical study reports and information to publish online.

Though there are various other activities carried out by the Eurotrials' Medical Writing SU in which I did not participate, my role as a member of the Medical Writing team allowed me to recognize that medical writers are involved in numerous activities across the clinical development phases, from the conception of a study (clinical study synopsis) to the final report of the study's findings and conclusions (CSRs), and including the development of clinical study protocols, patient informed consent forms and case report forms.

During my internship, the close relation between medical writing and biostatistics became clear. The frequent interactions with the Biostatistics department (responsible for analyzing and providing the study results, usually in the form of statistical analysis plans and reports) revealed essential to ensure that the study data were correctly interpreted and reported, as well as to clarify

any data issues. The latter point illustrates an additional important role in which medical writers play a part: quality assurance. When reviewing data from statisticians or directly from investigators, it is possible to identify errors that were not detected earlier. Thus, medical writers should seek to clarify the errors identified.

The primary objective set for this curricular internship was partially accomplished: I was able to acquire knowledge and experience in medical writing related activities, by actively participating in the development of articles, posters and CSRs. In general, I improved my ability to synthesize information, to interpret study data summarized in tables of statistical analysis plans and reports, and to present complex data in a simple and clear manner. Moreover, I became familiarized with the reporting guidelines applicable for each type of research study and with guidelines related to the development of CSRs (ICH-E3), acquired experience in using reference manager software (such as EndNote and Zotero), and in performing literature searches in various databases (Medline, Cochrane, Scielo).

I also had the opportunity to be involved in nearly all stages of the editorial process: the development of manuscripts, choosing the most suitable journal, formatting the manuscript according to the journals' requirements, and submitting the manuscript. The only step in which I did not participate was the peer-review process. This allowed me to become familiarized with the different stages of the editorial process and to realize that each journal has its own specific rules and guidelines for manuscript' formatting and submission (some journals may require the submission of tables and figures separately from the article, whereas others specify that the article, figures and tables must be sent in a single document). I also recognized that it is generally a good practice to define the most suitable journal before beginning the writing process, as it allows the manuscript to be developed in accordance to the journal's requirements (particularly in terms of maximum number of words and tables/figures, and overall structure).

Nonetheless, I was not able to acquire the level of knowledge and experience in biostatistics that I first set to accomplish, as my participation in the Biostatistics department was brief and mainly based on the development of statistical reports. Still, I was able to gain experience in conducting meta-analyses, both using RevMan and Excel.

Naturally, there were many challenges faced during my internship, related to the quick transition from the academic to the professional environment, my limited background on medical writing and the lack of experience in the development of scientific articles. The Problem-Based Learning (PBL) methodology adopted in the Bachelor's Degree provided me with a set of soft-skills that revealed

essential to overcome the challenges encountered and contributed to the overall success of my internship. For the quick transition from the academic to the professional environment, skills such autonomy, proactivity, and adaptability were of utmost importance, as well as the experience and availability of my colleagues to clarify any doubt. To overcome the lack of experience in the development of articles, I searched for and studied several reporting guidelines applicable for various types of article, which allowed me to become familiar with their general structure, the particularities associated with each one, and the essential information to be reported in each section. Moreover, reading the guidelines such as the ICMJE "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" and the GPP3's provided me a solid background on the principles that should be followed when developing and submitting scientific articles and to comply with legal and regulatory requirements. This greatly facilitated the development and submission of the articles I was responsible throughout the internship. Skills such as resourcefulness, critical-thinking and problem-solving were extremely helpful, particularly during the core project of the internship – the systematic review and meta-analysis – due to the many difficulties to overcome. These included the lack of an appropriate tool to assess risk of bias, the impossibility of carrying the analysis using a standard software allowing meta-analytic calculations, and the need to perform an initial correction to the values reported by both versions of the questionnaire. Moreover, one of the modules of the Master's Degree in Pharmaceutical Medicine ("Systematic Review and Meta-Analysis") provided me with essential background knowledge on this topic.

The multidisciplinary nature of the Bachelor degree in Biomedical Sciences and the Master's degree in Pharmaceutical Medicine revealed extremely valuable during the internship. The knowledge and terminology acquired in the fields of Pharmacology, Statistics, Physiology, Anatomy and Pharmacovigilance, allowed me to understand the scientific rationale behind each study, to interpret and critically assess the data I was working with, and to effectively communicate with my colleagues in the multidisciplinary environment that characterize CROs.

Additionally, the particular setting in which my internship took place (a CRO), allowed me to develop a set of valuable skills for the fast-paced environment of CROs. As each project had a deadline that needed to be met and because I was often involved in various projects simultaneously, I felt the need to improve my organization and time management skills, to allow me to keep track of my projects, identify which ones should be prioritized, and ultimately conclude the tasks assigned on time. On the long-term, this allowed me to become more productive.

Moreover, the recognition that poor performance may impact the company's business made me not only develop a sense of responsibility, but also improve my attention to detail and to review my deliverables more carefully. The independent quality control review of the documents I developed by my supervisor was also essential to ensure the quality and accuracy of my deliverables and to provide me with important feedback.

6. Conclusion

Overall, this internship allowed me to better understand the important role of medical writing in health research, as an essential tool to effectively, clearly and accurately communicate the data generated in research studies to various audiences, ranging from healthcare professionals to patients. I was also able to acquire practical knowledge on how to properly report various types of research and to submit the developed articles to scientific journals, so that their findings may be shared with other researchers and clinicians.

By complementing the knowledge acquired during the Bachelor's degree in Biomedical Sciences and the Master's Program in Pharmaceutical Medicine, the internship was a successful way to make the transition from the academic to the business world.

In conclusion, with the exception of acquiring experience in the tasks associated with the projects and services falling under the scope of Biostatistics, all objectives initially defined for this internship were successfully accomplished.

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