Universidade de Aveiro
Ano 2015
Secçao Autónoma de Ciências da Saúde

LILJANA GEORGIEVSKA

RELATÓRIO DE ESTÁGIO CURRICULAR EM MEDICAL WRITER NA BLUECLINICAL, PORTUGAL

CURRICULAR INTERNSHIP REPORT IN MEDICAL WRITING AT BLUECLINICAL, PORTUGAL

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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 científica da Doutora Cristina Lopes, Diretora de Operações Clínicas da Blueclinical, Investigação e Desenvolvimento em saúde, Lda e do Doutor Bruno Gago, Professor Auxiliar Convidado da Universidade de Aveiro.

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Professora Coordenadora S/ Agregacao, Universidade de Aveiro

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This thesis is the result of ten months work during which I achieved professional experience in Pharmaceutical Medicine at Blueclinical.

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Also I would like to extend my thanks to Dr. Bruno Gago for his input, advice and stimulating and interesting discussions.

My sincere thanks goes to Carina Bernardo for all the help, encouragement and friendship.

It was a pleasure to work with the colleagues at Blueclinical back office, as well as all the colleagues who work in Hospital da Prelada, which guided me during my practical work.

palavras-chave

Redação Científica, Medicina Farmacêutica, Ensaios Clínicos

resumo

O conteúdo deste relatório é um resumo das actividades realizadas durante o estágio de 8 meses, como escritor Médico Associado na Blueclinical, Ltd, em Matosinhos, Portugal.

As atividades desenvolvidas foram essencialmente relacionadas com a escrita médica, nomeadamente a escrita dos protocolos de investigação clínica, dos relatórios de ensaios clínicos, redação e preparação de apresentações de pósteres.

Além destas atividades, também tive a oportunidade de acompanhar um ensaio clínico de fase I desde o seu início até ao fim. Durante este estudo, foi possível conhecer de perto todas as etapas de realização de ensaios clínicos de fase I.

keywords

Medical Writing, Pharmaceutical Medicine, Clinical Trials

abstract

The contents of this report are a summary of the activities carried out during the 8-month internship as an Associate Medical Writer at Blueclinical Ltd, Matosinhos, Portugal.

Mainly my activities were related to medical writing, particularly writing the clinical research protocols, clinical study reports, writing manuscript and preparing poster presentations.

In addition to these activities, I also participated in performance of a clinical trial from beginning to end. During the period of its realization, I was able to familiarize myself with all the steps of the Phase I clinical trial.

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List of abbreviations

CRP	Clinical Research Partnership
R&D	Research & Development
PHI	Phase I
SOP	Standard Operating procedures
FDA	Food and Drug Administration
EMA	European Medicines Agency
GCP	Good Clinical Practice
ICH	International Conference On Harmonization
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
ICF	Informed Consent Form
CSR	Clinical Study Report
SAP	Statistical Analysis Plan

1.INTRODUCTION

This document is a summary of an internship-training period as an Associate Medical Writer at Blueclinical. The internship program is a part of the Master in Pharmaceutical Biomedicine, organized by the University of Aveiro, Portugal. The program is organised according to the Pharma Train European Training Syllabus for Pharmaceutical Medicine. Moreover, this program has been certified as a centre of excellence by the Innovative Medicines Initiative Pharma Train.

This practical curricular internship is part of the second year Master's Degree study. During this long-term curricular internship, the students have the opportunity to get hands-on professional experience of theoretical knowledge acquired in the earlier courses of the Master programme.

1.1 Internship objectives

The internship-training period began in October 2014 and ended in May 2015. The main purpose of this training was to develop required skills and acquire necessary knowledge to be a competent medical writer. In the Pharmaceutical Medical Writing Competency Model published in 2011, a group of medical writers describes the knowledge, skills, and behaviors they considered essential to become a successful medical writer. Therefore, during my internship I followed these guidelines to develop the necessary skills as a medical writer, which mainly consists of:

<u>Technical knowledge</u>

- knowledge of the techniques of scientific writing and editing
- having a necessary pharmaceutical (science) background
- familiarity with software and systems
- ability to train and mentor

<u>Technical skills and abilities</u>

- comprehend scientific concepts
- author quality documents

- perform project management
- edit documents
- interpret clinical and numerical data
- perform quality control
- review documents
- layout slides and posters

Behavioral skills

- being able to network
- having leadership and team working skills
- being detail-oriented
- having effective time management skills
- being organized

A medical writer needs to be curious, investigative, and reflective, as well as able to examine things from several angles. An important characteristic for medical writers is the ability to build relationships with clients and external experts, thereby developing the hard and soft skills are essential for the successful career (1).

Apart from medical writing, during my internship I was involved in several other activities in different areas related to medical writing. These objectives were planned to be achieved during the eight months internship and within different departments at the host company. The main objectives and activities planned for my curricular internship are underlined bellow:

- To be able to apply the knowledge acquired during the Master´s program
- Understand the functioning of a phase I unit
- Understanding all the phases of a phase I clinical study from pre-submission procedures to writing the final report
- Developing necessary writing skills to be able to perform medical writing

activities

- Understanding the data collection process in detail on a bioequivalence study
- Developing project management techniques

During my curricular internship at Blueclinical, I had an opportunity to follow a Bioavailability/Bioequivalence (BA/BE) study for one medicinal product from beginning to end. I was involved in performing the clinical trial from the point of protocol design to the final writing of the clinical study report (CSR). I also had an opportunity to be an active participant in all steps of the clinical study following activities of clinical trial assistants (CTA), PM activities, monitoring and clinical data management.

In this report, I have described the activities undertaken during my training period at Blueclinical, as well as all learning outcomes and skills acquired during this period.

The document has been divided in several chapters, starting with the explanation of the state of art in medical writing, the main objectives proposed for the training period, followed by with the description of the activities, and finishing with the decision and conclusion drawn at the end of the training period.

1.2 Host Company Overview - Blueclinical

Blueclinical Ltd. is a Portuguese privately held and independent medium-size enterprise that was founded in 2012 in Matosinhos, Portugal.

This company provides complete services that cover three sequential phases of the research and development of new drugs. The company consists of three major units: Blueclinical R&D, Blueclinical PHI and Blueclinical CRP(2).

Blueclinical R&D unit facilitates the clients by providing consultancy in the field of medicine and medical devices research and development via internal and external experts. Each project has a dedicated project manager to provide operational support and to contact internal and external clients.

The main activities of the Blueclinical R&D unit are underlined in the following tasks:

- Preparing and implementing preclinical, clinical and regulatory plans for new medicines, medical devices and other health products.
- Preparing and supporting the process of obtaining scientific and regulatory advice from competent regulatory authorities.
- Placing and monitoring preclinical studies.
- Preparing the investigator's brochure and investigational medicinal product dossier (IMPD).
- Preparing and submitting the clinical trial application to the competent authorities and ethics authorities.
- Preparing the investigator's brochure and investigational medicinal product dossier (IMPD).
- Planning, conducting and reporting clinical pharmacology clinical trials (Phase I) in healthy subjects or patients.
- Planning, implementing, monitoring and reporting therapeutic clinical trials (Phase II to IV) or observational studies with medicines or medical devices.

The **Phase I studies** are conducted in healthy volunteers and early stage studies in patients and in full compliance with the international regulations. The Blueclinical clinical team has experience and knowledge in performing diverse types of studies with generics (bioavailability / bioequivalence) and innovative medicines.

Studies in healthy subjects are conducted in Blueclinical's own phase I unit located at Hospital da Prelada, Porto. This unit is equipped with all necessary and modern facilities and highly qualified staff to perform the clinical trials. This unit is designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug in healthy people (volunteers).

Main activities of this unit are following:

- Bioavailability/Bioequivalence studies according to the requirements of the EMA, USA -FDA and other regulatory authorities
- Phase I studies with innovative medicines; drug-drug interactions, effect of food, dosage form proportionality, entry-into-man, and special populations

All activities are undertaken under international regulatory and ethical standards:

- Quality Management System compliant with EMA and US FDA requirements
- GCP-compliant as per inspection by INFARMED (EMA standards)
- Audited and qualified as service provider by various pharmaceutical companies

There is a short approval time of 3-4 weeks for regulatory review for Phase I clinical trials. It is beneficial that the Competent Authority (INFARMED) and Ethics (CEIC) reviews the clinical trials run simultaneously, which is more time efficient.

The main objective of Blueclinical **CRP** is to support clinical research activities of centres to achieve better efficacy and excellence in performing clinical research. This is achieved with the well-trained research teams, which are applying the best ethical and quality standards and applicable legal requirements. The research activities at the clinical sites supported by the Blueclinical stuff consist of:

- Supporting certification of investigators in clinical research
- Providing support to centres by the clinical research coordinators
- Providing quality research using standardized written standard operating procedures, which assure the compliance of good clinical practice and legal ethical requirements

Blueclinical has signed Clinical Research Partnerships (CRP) with twelve hospital centres and the northern primary healthcare units. In addition, investigators affiliated with research units managed by Blueclinical, who want to promote their own studies – Investigator Initiated Studies (IIS), can use Blueclinical's technical services from Blueclinical CRP.

The company has independent specific units where each of them have assigned specific tasks and duties, such as Medical Writing (MW), Business Development (BD), Data Management and Statistics (DMS) and Pharmacometrics (PHM). Figure 2 shows Blueclinical organogram by units and functions.

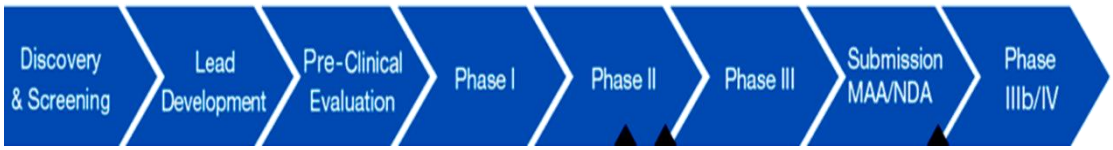

Figure 1. Phase of clinical development of medicinal drug from pre-clinical studies to post-market studies.

MP	Managing Partner
QA	Quality Assurance
HRA	Human Resources and Administration
SF	Support Functions (IT, HR, Administration)
COD	Clinical Operations Director
CRM	Clinical Research Manager
CD	Clinical Director
PHM	Pharmacy Manager
CTA	Clinical Trials Assistants
LM	Laboratory Manager
LT	Laboratory Technicians
RNC	Research Nurse Coordinator
RN	Research Nurses
PI	Principal Investigator
RP	Research Physicians
BDM	Business Development Management
DSM	Drug Safety Management
REG	Regulatory Affairs Management
MED	Medicines Unit
MDV	Medical Devices Unit
PM	Project Management
MWR	Medical Writing and Reporting
DM	Data Management
STA	Statistics
PKM	Pharmacometrics

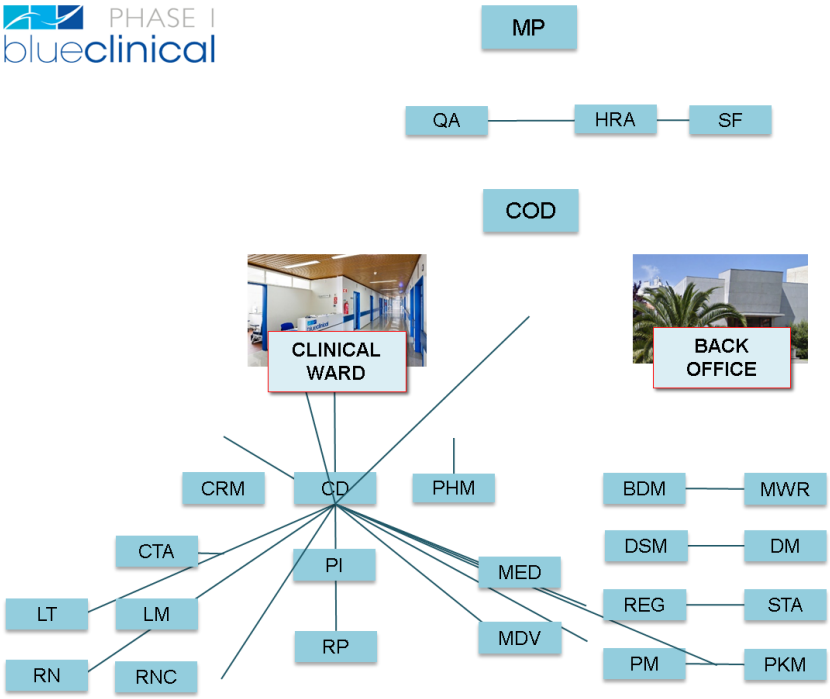

Figure 2. Blueclinical organogram representing the organisation structure.

1.3 State of Art

Medical writing has its roots back in time since the period when Hippocrates, Galen, Paracelsius and others recorded the diagnosis, treatments, prevention, prognosis and clinical correlations known at that time.

One of the first records about medical writing has been dated from the period of three centuries before the Common Era (CE), when Hippocrates wrote *On Hemorrhoids, On Fractures, On Ulcers, On the Surgery* and *On the Sacred Disease*. Galen was writing in Rome during the second century CE and he complied the medical knowledge of that period into an encyclopedic work.

Moreover, the work from Mainonides focused on diet, reptile poisoning and asthma during the twelfth century CE. Renaissance period is marked by the medical writing from Paracelsus, who described miners' disease and the treatment of syphilis with mercury. Additionally, his important contribution can be seen from the fact that he set the principles for future toxicology.

Another important writer who made a mark in history was Vasalius, who was acknowledged for producing the drawing of the human body and greatly advanced the study of human anatomy.

Harvey's contribution in medical writing was in 1600s when he described the circulation of blood in the body. This along with the book *The Principles and Practice of Medicine* written by William Osler defines the practice of medicine in the late nineteenth century (3).

1.3.1 Pharmaceutical Industry

The global pharmaceutical market has been rapidly expanding in the past decades and the need for the medical writers has been growing. This suggests a promising future for this job. Therefore, the training of new medical writers to accommodate future demands and to continue to provide the long-term quality service is essential. The medical writing in Europe and USA is a well-developed profession. On other hand Africa, the Middle East and Asia are in substantial need of medical writing but are currently underserved. This opens and creates new opportunities and challenges for medical writers (4).

It has been a tradition to conduct industry –sponsored clinical research in a few relatively wealthy locations in Western Europe, North America and Oceania. In the resent years, Portugal is becoming one of the countries that is more attractive for the sponsors to perform clinical trials. This is a consequence of the fact that Portugal has research capacity in terms of sufficient highly qualified personnel and the cost for performing the clinical trials is lower than in other regions.

As a result, the medical writer career is getting more popular as a profession and there is demand of more qualified persons in this field (5).

1.3.2 Communicating Medical Knowledge

Medical writers communicate an idea or concept to the readers in clear fashion. It is essential that they are able to explain the complex concepts and ideas clearly and accurately, and also try to engage the reader (6).

Medical communication is very important since it helps the public to understand the complex scientific findings. It also helps to share publicly through up-to- date information on policy relevant topics (7).

By 1970, English had challenged Latin as the language of institutional medical science and had become the dominant language of medical writing in England for communicating the new scientific discoveries. A very important milestone in the history of English scientific and medical writing is the foundation of the Royal Society of London in 1966.

The written communication as a means of dissemination of knowledge was particularly enhanced by the discovery of the printing technology. The medical publishing took off in 1640, and since 1660 over 150 books were printed per decade. The first scientific journals and periodicals were reported towards the end of the seventeenth century. Still medical knowledge continues to be transmitted in the handwritten form as well, as oral exchange of medical communication (8).

The original medical research can be presented in a format of several source document papers, reports or dissertations. In case of interpreting and analyzing the work from other researchers, the data is presented in form of literature reviews, opinion pieces or magazine articles. Particularly, it is important to emphasize the clear and precise style of

writing of these documents. Since the writers are often very familiar with their area of expertise, there can be a lack of clear explanation of their study in some cases. Hence, it is important to have a guide instructing how to build the solid structure for variety of written documents (9).

Nowadays, particularly useful tools for communication of new information are social media tools and platforms, which are evolving rapidly. Some of them are LinkedIn, Twitter and Facebook. They are an important part of communication of information among the health care professionals as more traditional ways of communication. This particularly is the case because of the fact that social media has a high speed of flow of information, high level of interactivity and global access of information. However, it is essential to approach the online world communication in the same way as a physical world, which means by using sound ground and common sense while processing new information (10).

1.3.3. Types of medical writers

Medical writing is a diverse profession and medical communicators can be writers, editors, proofreaders, project managers etc.

In general, the medical writers are classified as scientific and non-scientific. The scientific medical writers work on communication projects for medical professional or scientific audiences. In most of the cases they are very specialized in their area of work. On the other hand, the non-scientific medical writers' generally work on communication projects with less technical content like: health and medical articles for newspapers magazines, patient education material or marketing products etc. In general, these writers may write either for professional or lay audiences.

The medical writers engaged in regulatory medical writing in the pharmaceutical industry or CRO (Clinical Research Organization) have a clear job description. The medical writers working in the regulatory companies design and implementing regulatory strategies for the development and registration of new healthcare products. During the process of document development, they follow the standard operating procedures (SOPs) specifically created for each regulatory document.

The regulatory documents prepared by the medical writers include protocols, informed consent forms and clinical study reports. It is worth mentioning that there are

some differences in some regulatory guidelines between regulatory authorities in the USA (United States Food and Drug Administration -FDA) and Europe's European Medicines Agency (EMA). These differences in regulatory writing sometimes might lead to some challenges for regulatory writers.

The writers employed at the healthcare communication agencies target healthcare professionals and patients. They provide advertising, promotion and strategic guidance for the pharmaceutical industry. The main purpose of this medical communication is to raise awareness for new medicines via education and promotion. For that purpose, they use the traditional methods as well as implement digital communications using multichannel approach like development of websites, mobile applications, videos, digital television and other means.

The job of a medical writer in the communication agency is to produce wide range of materials from monographs, brochures, detail aids, posters, direct mail, symposium materials, press releases, peer-reviewed articles (in form of white paper) etc. (11).

Recently increased demand for health and medical information on the web and printed media has created a new niche for the medical writer, medical journalism. Medical journalists are informing the patients and general public with news related to diseases and treatment options through different mainstream media outlets. This can include the print media like newspapers, magazines, journals, brochures, leaflets, pamphlets, as well as web based media like healthcare portals, newsletters, blogs, e-learning platforms and other. These professionals filter the complex data according to relevance, and present them in language adequate to the targeted audience (12).

1.3.4 EMWA- European Medical Writers Association

EMWA is an association of the medical writer community in Europe, which provides a framework for professional medical writers. The association met formally for the first time in Brussels, Belgium on 21 February 1992. The first meeting was attended by 32 persons from seven countries. During that time, the structure and administration of the EMWA association was established.

The sufficient experience of a professional medical writer translates into quality. Hence the rigorous training and accumulation of experience helps in developing the good

medical writers. Since there is a high demand for quality knowledge based and medical information dissemination, this organization created workshops and certified medical writing training courses for medical writers.

The EMWA Professional Development Program (EPDP) provides high-quality training for medical writers. The courses consist of multifaceted workshops and homework assignments. The workshops are organized during the EMWA Conference in spring and autumn of each year. Employers honour the EMWAs EPDP in the medical writing community as valuable qualification. This is accomplished with a high quality level of workshops, as well as a sufficient standard of performance by participants to obtain credit for workshop competition.

At the 20th EMWA conference in Malta 2005 the foundation level and advanced level curricula were launched. The foundation level workshops were aimed for the new and relatively inexperienced writers. On the other hand, advanced workshops were planned and covered topics that were more suitable for experienced medical writers.

Today all EMWA workshops are assigned to one of the five options, each of which can be offered at foundation and at advance level. Those five options are:

- Drug Development
- Language and Writing
- Medical Communication
- Medical Science
- Professional Techniques

In order to gain credit for each workshop that will lead towards obtaining and EPDP certificate, each workshop leader needs to prepare analysis questionnaire, a pre-workshop assignment, and a workshop and post-workshop assignment.

2. MONODISCIPLINARY ACTIVITIES – MEDICAL WRITING

Medical writing is an important profession and recently their demands have increased. Medical writing is a complex field since the writers need to possess particular knowledge and skills to be able to deliver well-written, clear and accurate scientific documents. There has been also significant development in many medical fields and the numbers of research studies have increased. All this has led to greater demand for medical writers, who will communicate the findings to an increasing audience (13).

Based on the type of medical writing, in general medical writing can be divided into two groups; regulatory and scientific medical writing.

The regulatory medical writers are in charge of writing all the documents that accompany the process of approval of new medicinal products, which include: Clinical Trial Protocols (CTP), Informed consent forms (ICF), Clinical Study Reports (CSR) etc.

The scientific medical writers also write informative documents such as publications, poster presentations, brochures etc.

2.1 Synopsis

Synopsis allows the reviewer to get a panoramic view of planned clinical trials. The origin of the word synopsis is derived from (Greek word, sun - together, opsis - seeing) means brief summary of something. The research protocol synopsis is reviewed by the IRB members, who might determine the potential issues. It is not a rare case that investigators write the synopsis after the whole protocol has been written, without having the opportunity to see if the study is feasible or needed (14).

The consisting parts of synopsis are:

- trial title and protocol number,
- background and rationale,
- trial objectives,
- study design and duration,
- total number of sites ,
- list of investigators,
- sample size,

- patient population,
- inclusion criteria,
- exclusion criteria,
- drug formulation,
- dosage regimen,
- washout period,
- pre-study screening and baseline evaluation,
- treatment assessment visits,
- concomitant medication,
- rescue medication and risk management,
- premature withdrawal,
- efficacy variables and analysis,
- safety variables and analysis and statistical analysis.

During the period of my internship training, I was engaged in writing two synopsis, first for the clinical trial and the second for the observational study.

The key elements of the strong synopsis are to define design of the study, measurable objectives, develop a hypothesis and to start with a clear research question.

Observational studies are studies in which the causes, preventions and treatments for outcomes are studied. Depending on the case they are covering, they can be prospective or retrospective observational studies.

In most cases, the observational studies are post-market studies performed to collect additional information about the efficacy of the therapy/drug.

In practice, the four following types of observational studies exist:

- Cross-sectional: patient populations included in these types of studies are examined at a single point in time and there is no consideration regarding any changes that may have occurred over time.
- Case-control: the relation between multiple exposures and the outcome is explored. These studies are retrospective, where investigators rely on records and patients recalls to understand their exposure. In this case there are two groups of patients enrolled: the cases and the controls.

- Cohort: This type of observational study examines multiple health effects and exposure based on their follow-up over time to check for outcome occurrence.
- Ecological: this type of study examines the relationship between exposure and outcome, at a larger scale instead of an individual one. In this case, the investigator maybe able to analyze trends in the large group of people regarding health conditions.

During my training, I wrote a synopsis for the retrospective observational study performed at Hospital da Prelada. In this study, the efficacy of several different combinations of medication treatments was investigated for a prolonged period of time.

2.2. Protocols

During my internship training at Blueclinical, I had the opportunity to write two clinical trial protocols- CTP. Execution of the clinical trial cannot begin without written clinical trial protocol. The basis of a clinical development program is the trial protocol. Therefore, when writing a sound clinical trial protocol it is necessary to have a good understanding of the ICH guidelines. The origin of the name protocol comes from (Greek word, protokollon - first page), which means a format procedure for carrying out a clinical research/trial.

A protocol for a clinical trial is a detailed plan, which describes objectives, background methodology, organization, the participants, interventional procedures and assessment tools of the trial. The protocol is the 'operating manual' for the clinical trial. Its importance is essential since following the protocol will ensure that all of the researchers will perform the trial in the same way on patients with the same characteristic (19). Moreover, during the course of development of the clinical protocol there might be some protocol amendment needed on ongoing basis.

One of the protocols was for a clinical trial of BA/BE clinical study the medicinal product, which was conducted in accordance to the EMA's regulations.

Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie

within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy.

According to EMA's regulations, the standard design is a two-way crossover design. The washout period needs to be sufficiently long (at least 5 times the terminal half-live). If the SmPC says the product shall be taken with food, the study shall be performed under fed state; otherwise, in fasting state. The test product used in the study should be representative of the product to be marketed and this should be discussed and justified by the applicant.

Majority of the clinical trials in the company are Phase I bioequivalence studies. Having said that there is an already a created general protocol template which was easy to follow and to make necessary modifications for the final new version.

The protocol was written on the base of an already written summary for the same clinical trial, which was presented and approved by the sponsor.

While accomplishing this task I learned to:

- use the style guide and protocol template
- manage the timeline for protocols and their amendment, including internal and external review
- navigate the protocol synopsis, using it as an outline for the protocol
- describe the requirements for and elements of a protocol including the hypothesis, clear and concise objectives, primary and secondary endpoints, inclusion/exclusion criteria
- develop protocol amendment

2.3 Clinical Study Report (CSR)

The Clinical Study Report (CSR) in Europe (EMA) or Clinical Trial Report (CTR) US FDA, is a critical document in the drug development and regulatory submission process.

The Clinical Study Report (CSR) is a document where all the clinical and statistical analysis are integrated and presented in a single report. In this report the tables, figures and appendices, sample case report forms, information related to the investigational

products, technical statistical documentation, patient data listings, and technical statistical detail etc. are incorporated.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in 1995 produced a tripartite harmonised ICH guideline on the format and content of a study report to be acceptable in all three ICH regions (15).

The listing of the documents that medical writers need to have to be able to write the complete Clinical Study Report is as follows:

Tools and Administrative Information

1. Protocol number or study number
2. Study number in ClinicalTrials.gov
3. Number and name of each clinical study site or centre
4. Sponsor's in-house style guide, if applicable, and published style guide, if applicable
5. Clinical study report template in Microsoft Word, if available
6. Adverse event (AE) and/or serious adverse event (SAE) narrative template, if applicable (ie, if there were AEs and/or SAEs reported in the clinical study, and if those events will be written as narratives for inclusion in the CSR)
7. Clinical study report project timeline
8. For interim reports, the cut-off date for clinical study data to be presented in the interim report
9. Name, title, and contact information for sponsor's representative who will approve and sign CSR
10. Description of naming conventions for clinical study report files, if applicable
11. Names and contact information of sponsor personnel with whom the writer will work to draft the CSR
12. Information on how to store, archives, and circulate draft and final CSR, if applicable
13. Directions as to who will store, archive, and circulate draft and final CSR

14. Decision from the sponsor as to which investigational product name will be used consistently in the CSR, if applicable (especially if the product name has undergone changes since protocol was written)
15. Names and addresses of CROs used and description of their role in the study, if applicable
16. Sponsor's content- or process-related SOPs that apply to writing clinical study reports
17. Description of sponsor's ideal label for the investigational drug product (optional)
18. Clinical development plan (optional)
19. ICH Guideline E3, The Structure and Content of Clinical Study Reports
20. FDA Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications, if applicable
21. European Medicines Agency (EMEA) – Note for Guidance on the Inclusion of Appendices to Clinical Study Reports in Marketing Authorisation Applications, if applicable

Content of CSR

File folders as content

1. Clinical data as tables, listings, and figures (TLFs)
2. Screening logs for subject disposition (if not provided in TLFs)
3. Case report forms (CRFs) of subjects who had serious adverse events (SAEs)
4. Milestone study period dates: dates when first subject enrolled, last subject enrolled, and last subject completed study
5. List of IRBs/IECs/DMC addresses and chairperson's name
6. Sample study-specific master Informed Consent Forms for protocol and all amendments
7. Study-specific case report forms (CRFs)
8. Safety (AE and/or SAE) narratives, if applicable
9. Statistical Analysis Plan (SAP; sometimes called the Data Analysis Plan, or DAP), if applicable

10. Pharmacokinetics (PK) report, if applicable
11. Pharmacodynamics report, if applicable
12. Toxicology report, if applicable
13. Immunogenicity report, if applicable
14. List of references (abstracts or manuscripts) from publications derived from clinical study data
15. PDF files of all medical literature supporting the study and cited in the CSR
16. Original clinical study protocol and all amendments (strongly preferred as Microsoft Word files)
17. Investigator brochure (versions used in the study, preferably as Microsoft Word files)
18. Chairperson and address of DMC/Steering Committee, if applicable
19. List of site names, numbers, and locations
20. Name of the company that managed the clinical trial supply
21. Names and addresses of laboratory facilities used
22. Laboratory certificates and normal ranges for all laboratories
23. Investigators' CVs (as PDFs or scans)
24. List of investigational drug batch numbers and list of subjects (by subject number) receiving each batch of investigational drug (Note: This is often the hardest information to acquire for the CSR.)
25. List of protocol violations and/or deviations (if not included in TLFs)
26. List of investigators and study personnel, mailing and e-mail addresses, telephone and fax numbers; if lead principal investigator, identify and include contact information
27. List of names and contact information of sponsor's personnel who participated in the clinical study: medical monitor (usually an MD), biostatistician, and clinical research associate(s) (16).

During the practical training, I had an opportunity to learn the elements of the CSR and the appendices by actively been included in developing clinical study reports for the investigated medicinal product. I learned the methods to turn the protocol and statistical outputs in cohesive document, as well as which guidelines to follow during document

preparation. The main achievement of this task was to learn how to turn the protocol and data into clear concise submission documents. I learned to describe the elements required for the CSR and appendices, handling the results and statistical analysis and utilizing the guideline and template for writing the Clinical Study Report (15).

2.4. Creation of an Abstract and Poster Presentation

Part of my medical writing experience was to prepare the poster presentations for the scientific conference. The scientific poster is a communication tool, which combines a verbal presentation with visual aid (16).

When developing a poster, we have to take into account other skills that are not always present when writing a scientific article (17).

Writing abstract for the conference required following certain guidelines for example an exact word limit. It is important while writing the abstract to use the active voice and it is preferred to use generic rather than trade names of the drugs. Also the styles of abstracts for original studies can vary depending on the research. Hence, guidelines exist for reporting manuscript abstracts for various types of original research (CONSORT,13–15 IDCRD,16 PRISMA,17 QUOROM, and STROBE18). These guidelines can be very helpful in providing a clear format for an abstract writing (18).

It is particularly important when writing the abstract to pay a lot of attention to the title. The general rule is that the title should not be more than 10-12 words. It should clearly describe what was investigated and how it was done.

Once the abstract was accepted the next job was to prepare the poster presentation. In preparing the poster, both the content and the visual presentation are important. It is helpful to use the rule of 10s: since the average person scans the poster for 10 seconds from 10 feet away.

The rules for preparing and submitting the poster presentation for the conference have specific instructions and strict guidelines. I followed the online guidelines from the conference website and referred to the examples for the poster preparation. The application was online with preset field and word counts. Since the poster presentation is a very brief presentation of the work, it is important to present the most interesting piece of the study. In general, the material is prepared in PowerPoint or an equivalent software.

The general instruction of poster preparation is to keep the sections of the posters short and simple, which allows an easy read.

While developing the poster presentation it is very important to consider the following topics:

- Title – should be effective and quickly attract and orient the audience;
- Sections – Their sequences should be well defined and easy to locate in the poster;
- Content – Should be concise but the message must be clear;
- Time – The poster should be short enough so it can be quickly read;
- Visual aids – Long sentences should be avoided and the use of images,
- Graphs and drawings should be supported;
- Others – Several other points should be considered such as colors used, font type and size, background, spacing,

2.5. Manuscript Writing

During my internship period, I was involved in activities associated with the preparation of publications for the international peer-reviewed journal. The first step is to analyze the clinical trial report and prepare the outline for the manuscript. It is very important to be able to synchronize and adjust to the client's needs. The second step is developing the manuscript to define what needs to be included in the publication, accompanied by a third step, which decides what, will be the target journal where planned results will be published. Consequently, I checked the guidelines for the authors for the target journal. The first draft of the manuscript was developed following these guidelines. Data from the study were presented in a clear and understandable manner with reference manager used for reference organization. I was able to write a couple of different manuscripts during the internship ranging from observational studies, to systematic reviews and meta-analysis.

This task was particularly important for development of my medical writing skills. In particular, I paid special attention in developing skills and knowledge related to the systematic reviews manuscripts. For that purpose, I performed a literature search in several

databases and learned to perform the statistical analysis (meta-analysis) in specialized RevMan software in Cochrane library.

3. MULTIDISCIPLINARY ACTIVITIES

Throughout my internship, I had the opportunity to participate in a wide range of activities that gave me the chance to develop diverse skills and working experience in different disciplines.

In the section below, I will describe those performed activities structured in several subsections: SOP training, sample size calculation, performing clinical trial at Hospital da Prelada, clinical data management and medical writing training at the EMWA Conference at Florence, Italy 2014.

3.1 SOP training

Significant improvement of quality or research and reducing the cost by pharmaceutical companies can be achieved by following certain sets of procedures called ″Standard Operating Procedures″ (SOP). The SOPs are regulatory requirements in the Pharmaceutical Industry, which are essential for any clinical trial plan effectiveness and efficiency. It has been reported that a typical pharmaceutical industry has on average from 1200 to 1300 SOPs.

SOPs are written instructions that document a routine or repetitive activity, to be followed by employees in an organization. For each specific job description, there are specific SOPs. In addition, there are common or general SOPs, which are valid for all employees.

Their importance is seen by the fact that they facilitate consistence and conformance to technical and quality system requirements, and also help support the data quality.

As a medical writer at Blueclinical, I needed to undergo the training of general SOPs and specific SOPs designed for medical writing department. Additionally, I needed to get familiar with some additional SOPs from other departments, which were relevant in performing my task at Blueclinical. Therefore, the first task upon my arrival at the company was to get acquainted with the company's SOPs, and to get familiarized with the task and duties and company's activities (19).

3.2 Sample size calculation

The determination of the sample size during the planning stage of the clinical study is important for assuring validity accuracy, reliability and integrity of the intended clinical study.

Determining accurate sample size is important to get significant power for detecting a clinically meaningful difference among treatments as well as the trade-off between cost effectiveness and power if any.

Often the statistical evaluation for sample size calculation is performed based on some statistical inference of primary study endpoint with certain assurance. The sample size calculation can be classified into sample size estimation/determination, sample size justification, sample size adjustment and sample size re-estimation.

During my internship at Blueclinical, I had an opportunity to participate in the process of sample size calculation for a Phase I bioequivalence trial. Primarily I performed the literature search for similar phase I studies of specific molecule in Clinicaltrials.gov. The information for the tested molecule intra-subject coefficient of variation and sample size used were retrieved. Subsequently this information was used for R statistical program to calculate the number of individuals needed for a particular clinical trial.

The subjects sample size was adjusted for some factors as dropouts in order to yield sufficient number of evaluable subjects for statistical evaluation of the drug studied.

This task gave me the opportunity to learn new database searches, retrieve the information needed and helped me in process of sample size calculation for a phase I clinical trial in a most efficient way. This is particularly important since estimation of the sample size is laborious and time-consuming process of data guttering (20).

3.3 Clinical trial- Hospital da Prelada

Drug research and development is costly and lengthy process, but necessary to demonstrate the efficacy and safety of the drug product, under investigation. It is also important to insure that the studied drug possesses the identity, strength, quality, purity, and stability after its approval (21).

Clinical trials need to be designed with a number of parameters in order to generate meaningful results. These parameters are the subject population that need to be studied, treatments to be investigated, endpoints and the methods by which the trials will be conducted (21).

Bioequivalence is a term in pharmacokinetics used to assess the expected in vivo biological equivalence of two proprietary preparations of a drug. In 2003, Birkett defined the bioequivalence stating that two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailability's (rate and extent of availability) after administration in the same molar dose are similar to the degree that their effect, with respect to their efficacy and safety, can be expected to be essentially the same. According to the regulations applicable at the European Economic Area, bioequivalence is demonstrated if the 90% confidence intervals (90% CI) of the ratios for AUC0-t and Cmax between the two preparations lie in the range 80.00 – 125.00% (22).

In order to become familiar with the process of performing the Phase I clinical trial during my internship at Blueclinical, I followed the entire process of performing the clinical trial.

The objective of this study was to determine and compare the relative bioavailability and thus the bioequivalence of Test formulation in comparison with the Reference formulation, after single-dose administration and under fasting conditions at Hospital da Prelada. This allowed me to establish logical and coherent thinking about the required tasks. The pharmacokinetic studies were conducted at the Hospital da Prelada on Floor 3, where facilities of Blueclinical are located.

Before the clinical trial began, every member of the team did an online training related to the protocol. After finishing the training there was an evaluation questionnaire, which each participant in the clinical trial needed to pass the test in order to be able to participate in the clinical trial.

3.3.1 Recruitment of volunteers

I was present when the recruitment process was performed for one of the clinical trials at the Hospital da Prelada. Initially, the Blueclinical database of potential volunteers with certain required criteria (exp. no smokers etc.) were searched. Consequently, to check

for their availability in order to participate in the trial, potential volunteers were contacted via telephone.

3.3.2 Screening of the patients

Healthy volunteer subjects were screened and their vital signs were assessed. Screening period consists of a period of time used to assess the subject's compliance with the protocol criteria. The investigator than needed to check all results from the test and to make the final decision which volunteer could participate (some were excluded from the trial due to the medical conditions).

The responsible investigator checked all the results and the suitable candidates were selected and to whom numbers were allocated. These numbers were used for the identification of the subjects for the trial purposes. The information that was shared with the sponsor/CRO never contained the participant identification but only the subject number.

3.3.3 Obtaining informed consent

The subjects and the investigator signed and dated two copies of the informed consent form (ICF) (one copy stayed in the volunteer dossier, and the other one was for the volunteer. It was obligatory that the document was signed and dated by the volunteer himself.

3.3.4 Dosing of the subjects

The handling of the trial medication was performed in the pharmacy, located inside Blueclinical Phase I unit at Hospital da Prelada, and the dosing activities were performed under GMP-like conditions.

The pharmacists needed to ensure that:

- IMPs were appropriate for use and were procured, handled, stored and used safely and correctly
- IMPs were managed and dispensed to subjects in accordance with the duty approved current protocol
- all pharmacy clinical trials procedures comply with relevant guidelines and regulations

The temperature and the humidity in the pharmacy, were regularly monitored and recorded. The IMP storage areas were fitted with calibrated temperature monitoring devices that recorded minimum and maximum temperatures, and had a system to alert staff if the temperature fell outside of the specific range. The temperature monitoring devices had a valid calibration certificate that was maintained for reference.

The pharmacist did individualization of the medications at the Pharmacy, which is part of the Blueclinical. The Quality Assistant performed the quality control of the labels used for labeling of the medicinal products. There was a flowchart to follow, where all the performed activities were divided by date and time. When activity was done the box was checked, to signified that the task was finished.

3.3.5 Sample collection

Serum /plasma concentrations were obtained at regular intervals at the sampling time indicated at the study protocol.

Plasma concentrations were used to estimate the following pharmacokinetic parameters: Maximum observed plasma concentration (Cmax); time of occurrence of Cmax (tmax); area under the plasma concentration versus time curve (AUC) from time zero (predose) to the last sampling time with quantifiable concentrations (AUC0-t); AUC from time zero to infinity (AUC0-∞); residual area or percentage of extrapolated part of AUC0-∞ (%AUC); apparent terminal elimination rate constant (λz); and apparent terminal elimination half-life (t1/2).

The ln-transformed Cmax and AUC0-t were the drug pharmacokinetic parameters of interest for the bioequivalence assessment. The other parameters were calculated and provided for information purposes only.

Each collection material (tubes, urine containers etc.) was labeled with the subject identification number, time point etc. In this way, the nurses were able to collect the samples and were able to easily identify to which subject they belonged to. After collection of blood samples, they were placed in a box with ice. The lab samples for safety analysis were immediately transferred to the Hospital da Prelada Central Laboratory for further analysis. The blood samples collected for PK analysis were processed and stored at Blueclinical Phase I unit until their shipment to the qualified biolaboratory partner.

All the blood samples and urine per time point were collected as defined in the study protocol. This activity was very useful for future reference for the medical writing of clinical study protocols and clinical research reports.

3.4 Clinical Data Management

I spent a part of my training at Blueclinical at Clinical Data Management Department. There I had the opportunity to see different steps of the clinical data management process. In one study, I took part in designing a Case Report Form (CRF) in both the paper format and the electronic one.

Clinical Data Management is a crucial phase in clinical research, which leads to the generation of high quality and reliable statistical data from clinical trials. It consists of collecting, cleaning and management of subject data in agreement with regulatory standards (23).

The CDM includes various procedures from designing the Case Report Forms (CRF), CRF annotation, database designing, data-entry, data validation, discrepancy management, medical coding, data extraction and database locking. Nowadays there is an increased demand to improve the CDM standards to be able to meet the regulatory standards and to be able to outcompete the competitor in product commercialization (23).

The quality of generated data has an important role in the quality of the performed study. The quality of data is obtained by minimizing the number of errors and missing data and also by collecting maximum data for analysis. This was facilitated by the use of software applications (exp. VIEDOC), which increases the speed and precision of data management, as well maintains an audit trail and provides easy identification and resolution of data discrepancies. Many different software tools are available for data management and they are Clinical Data Management Systems (CDMS). Mostly CDMS used in the pharmaceutical companies are commercial like ORACLE, CLINICAL, CLINTRIAL, MACRO, RAVE and VIEDOC. Among the open sources, the most used one is OpenClinica, but at Blueclinical, I used the VIEDOC software.

During regulatory submission it is very important to maintain the audit trial of data management activities as well management of discrepancies (24).

To meet this objective, best practices are adopted to ensure that data are complete, reliable, and processed correctly. Also the CDM has its guidelines and standards in electronic data capture that need to be followed. Therefore, the electronic records need to comply with the Code of Federal Regulations (CFR), 21 CFR Part 11. This regulations request the use of validated system to ensure accuracy, reliability and consistency of the data (25).

CDM is integrated in all steps of a clinical trial, from the beginning when the trial is planned until the last part when the final report is written.

In the beginning of the study the protocol serves as a base for the designing of the Case Report Form (CRF) (printed, optical or electronic version). CRF needs to be well designed to give opportunity for sufficient and necessary data collection and data management. With this said, the data collected need to be accurate and suitable for statistical analysis.

During the development of the CRF the ICH-GCP guidelines and data management specific guidelines are followed.

At Blueclinical, I followed the standard form for CRF earlier developed in the group to design the paper format of CRF, which afterwards was used for developing the electronic version of CRF. It is necessary to spend sufficient time and care in proper development of CRF since that will save a lot of time and unnecessary worries during the time course of the trial.

Therefore, it is especially important to take into account proper wording, layout of the CRF, coding and which kind of questions will be asked and to minimize the repetition in the form. Even though there is freedom in designing the style of the CRF form depending on the clinical trial, there are some common parts found in all CRF. The common sections are mainly centered on medical history, concomitant medication or adverse events recording.

After designing the CRF based on the clinical study protocol (CSP), the Data Management Plan was written. The Data Management Plan is a written summary of the whole process of CDM. If someone needs to know something about the CDM process, namely task as CRF development, study setup, CRF flow and tracking, data entry, data cleaning, coding, reports, data transfer or database lock, they should look at this document.

The main purpose of this document is to have a registry in case someone new starts to work in the study or if an auditor or inspector wants to know something about the CDM procedures of that specific study or where to find the documents regarding a specific CDM procedure. In short studies, such as bioequivalence studies, which last approximately 4 to 6 months, this document is not indispensable. However, for long studies, which last for a period of a years and where the CDM teams constantly change, it is the best way to assure consistency between procedures and traceability. The final data collection instruments (CRF and others such as patient's diaries) are also developed and implemented during the study setup, according to the CRF structure previously developed.

Regardless of the type of CRF used (paper or electronic) the final place where the data will be stored is in a computerized system, containing one or more databases. A database could be any kind of structured set of data, which includes spreadsheets or other types of structured data formats. For regulated clinical trials, although the intermediate output could be found in other formats such as ODM-XML, the final repository of data is generally in the format of SAS® datasets, according to predefined standards in order to be sent for analysis by regulatory authorities. Database development is also the responsibility of the CDM department before the study starts. When an electronic system is used as platform for the CRF, database design is usually achieved by an annotated CRF, which is the same as the CRF structure specifications but with the annotations of the variable names in the database and other descriptors of the characteristics of the field (numeric or not, visible or not, etc.).

Clinical data introduced in the database must be validated, so a Data Validation Plan is also developed and implemented at this stage. Validations (also known as edit checks) could be implemented directly on the CRF if an electronic platform is used and/or performed by an external program. Validations include, but are not limited to, decimal places limitation, visibility conditions, or logical conditions (such as preventing dates from being introduced in the future or illogical answers). The DVP has all the validations recorded for implementation and posterior analysis for quality control and assurance purposes. Also, it is good practice that before the study is set for data entry a training document with completion guidelines are available for the ones who will enter the data. Those guidelines should not contain instructions that lead the user answer, but give some indications to prevent entry errors and to assure that all the fields are correctly filled. After

all the tools and documents are in place, the database or the CRF if using a CDM platform, should be tested and those tests documented in order to assure that is everything according to what has been planned.

3.5 Training at European Medical Writing Association (EMWA)

I had an opportunity to attend the European Medical Writing Association (EMWA) Conference, in November 2015, and held in Florence, Italy. During this event, I also had the opportunity to follow three workshops: Subject Narratives, Orphan Drugs and Writing Risk Management Plans. This gave me an opportunity to increase my knowledge in these areas of medical writing.

3.5.1 Subject Narratives Workshop

During this workshop, what was most emphasised was the importance to harmonise way of gathering important clinical safety information that arise during the clinical development.

In particular, the subject narratives can be explained as a brief deception of safety events of particular interest in an individual patient enrolled in a clinical trial. It is important to find all the necessary data in one place since the summary data usually does not provide integrated information on events in individual subjects. Also, the listings are often laborious for the reviewer and extensive discussion about circumstances surrounding an event may be too detailed for the CSR.

The subject narratives' can be designed in two major formats: as text only and programmed header plus text format. However, it is worthy to mention that there is not an official definition or requirement for narrative format. In fact the narratives are a key safety data presentation, alongside data summaries and listings.

The Guidelines of ICH E2A on Clinical safety data management defines AEs, ADRs, seriousness, expectedness. Also it defines data required for reporting, including: patient data, suspected IMP, other treatments, suspected ADR and reported assessment of relatedness.

ICH E3 is an important guideline, which defines the events and lists information, which is crucial to be included in the narratives.

It is very important to define the process of writing subject narratives before actually starting to write. In particular, it is important to define the format (programme or text only), decide which event in which patients need narratives, discuss approach and content with team, write 5-15 prototype narratives, make a team review and finally take care of the quality control of narratives.

The subject narratives are written to describe the safety events of particular interest: deaths, serious AEs and other serious significant AEs that are judged to be of interest because of clinical importance.

The contest of subject narratives consists of patient identifier (age, sex), general clinical condition, the disease being treated and its duration, relevant concomitant and previous illnesses, with details of occurrence and duration, relevant concomitant and previous medication with details of dosage and test drug administered, dose and duration.

Sources of information for writing subject narratives are: clinical trial database, case report form, pharmacovigilance database/ SUSAR reports, hospital records and autopsy reports. It is important to have agreement with the client who will extract data since this process can be time consuming and most of the time not available especially for external writers.

3.5.2 Risk Management Plan Workshop

During this course I received the practical knowledge and experience in writing the Risk Management Plan (RMP) as a part of the workshop activities. This workshop was particularly interesting and useful since it is highly important in each pharmaceutical industry to develop a Risk Evaluation and Mitigation (REMS) plan to ensure that the benefits of a medicine outweigh its risks.

Moreover, in many countries a special medicine safety plans may be required as a part of medicine approval process in order to retain its approval status.

RMP is submitted to the Health Authorities with an application for a new marketing authorization, with periodic Safety Update Reports (PSUR) as a stand-alone document. This document is legally binding and once the RMP is accepted by the Health Authorities, the Marketing Authorisation Holder (MAH) has a legal obligation to perform the activities described in the RMP.

The RMP is prepared at the time of request for approval of a new drug, new indication, new patient population etc. and the need to be submitted with the submission dossier. In addition, this document is prepared when a significant new safety concern is identified or at the request of health authorities.

The pharmacovigilance and risk management activities that might be included in a RMP fall into two categories: routine activities (which would generally be conducted for any medicine at same stage of development) and additional activities (which are designed to address identified safety concerns).

Under routine pharmacovigilance, the safety evaluations integrated in clinical trials, as well the monitoring and reporting of spontaneous adverse events pre-approval is considered. The main objective of the routine risk management activities is to ensure that adequate warnings are included with all product information and packaging of the medicine has a careful labelling.

The action plan of RMP might consist of additional pharmacovigilance. This can include different forms like:

- active surveillance (e.g. medical record review etc.),
- epidemiology studies (retrospective or prospective),
- further clinical studies (e.g. specific studies or larger studies over longer period)
- drug utilization studies (how the drug is marketed, prescribed and used in specific
- population often stratified by age or gender) and
- how all this factors influence on the social, economic and clinical outcomes.

Different parties are involved in risk management plan: patients, health care professionals, regulators, pharmaceutical companies etc.(26).

The outcomes from following the Risk Management Plan writing workshop at EMWA Conference were that I learned how to write the RMP plan, which is an essential skill for every medical writer who wants to pursue the carrier in the regulatory writing.

3.5.3 Orphan Drugs

An orphan drug is a pharmaceutical drug that is intended to treat diseases so rare that sponsors are reluctant to develop them under usual marketing conditions. Most of the rare diseases are genetic and are present throughout the person's entire life. It is worth mentioning that no single cutoff number has been agreed upon for which a disease is considered rare.

By EU definition the orphan drugs are defined as a diagnosis, prevention or treatment of a life threatening or chronically debilitating condition in ≤ 5/10 000 persons in the EU, or less than 250 000 patients per year. These medicinal products are unlikely to be marketed without incentives and notable benefit expected. To qualify for an orphan drug the drug also needs to be of significant benefit to those affected by that condition. Furthermore, there is no existing satisfactory method of diagnosis, prevention or treatment authorized in the EU.

The assignment of orphan status to a disease and to any drugs developed is the matter of public policy in many countries. It is mentioned in Thomas Reuter's publication from 2012 ″The Economic Power of Orphan Drugs″, that there has been an increase in investigation in orphan drugs Research and Development due to the U.S. Orphan Drug Act (ODA). The period between 2001 to 2011 was the most productive for orphan drug approvals.

The European Union (EU) has a legislation named Regulation (EC) No 141/2000, in which the medicinal products developed to treat rare diseases are referred to as ″orphan medicinal products″. The latest is a Directive 2011/24/EU on the application of patients' rights in cross-border healthcare.

The Committee on Orphan Medicinal Products of the European Medicines Agency (EMA) administers the EU legislation. The orphan drug status granted by the European Commission gives marketing exclusivity in the EU for 10 years after approval. In 2007 the FDA and EMA agreed to have a common application process for both agencies, which will reduce the burden on manufacturer who apply for the orphan drug status.

While attending this workshop I acquired the knowledge about orphan drugs legislation procedures in different countries. Also I learned how to prepare the EMA orphan drug designation and procedure for applying to the COMP for the approval. In

addition, I learned what are the necessary documents for orphan drug application as well as protocol assistance and scientific advice.

4. DISCUSSION

4.1 Task assigned

The tasks during my internship were assigned to me sequentially so I was able to focus on each one individually most of the time. However, in some instances when a new project required a task that I did not perform before, I was organizing my time to accommodate the two tasks simultaneously.

The focus of my training was on medical writing but I performed some tasks in other departments as well. Very useful in task planning and organization of the workload was the company electronic platform and Monday morning meetings. This system helped me to be more organized and to efficiently track the deadline of various tasks. The majority of tasks during my internship at Blueclinical were performed in the Medical Writing Department, Clinical Data Management Department and at the Hospital da Prelada.

4.2 Learning outcomes

During the training period, I had an opportunity to enrich some of my hard and soft skills. For the hard skills, I was able to develop technical skills that help me in medical writing particularly mastering to work in new programs like reference manager software and statistical programs RevMan for performing the meta-analysis and using different databases for reference search. Moreover, I developed new medical writing skills. In particular I got more knowledgeable about writing clinical trial protocols and clinical trial reports. Additionally, I understand and use national and international regulatory guidelines and laws. This allows me to further develop my medical writing skills, to be able to use adequate and new vocabulary as well as applying adequate structure format and delivering the proper final message. Moreover, the medical writing is a wide discipline and even though I do improve, my medical writing there is still room for improvement. In parallel, I was afforded the opportunity to perform medical communication and regulatory writing. This enabled me to experience both slightly different medical writing disciplines, which enrich my medical writing skills in many ways. Additionally, I developed other skills, which were related with the ability to use the clinical data management software for clinical data collection and data processing.

On the other hand, from the soft skills I believe that I developed and improved some skills that are crucial for teamwork in the company setting. Mainly those are the cluster of personality traits like interpersonal skills and communication with other colleagues. Also in the company setting it is important to be able to work under pressure and to finish an urgent job and hit the challenging deadlines. This is particularly important when dealing with the clients in a private company. I learned to be more decisive and to punctual which helps to achieve the maximum results in shortest period of time. However, since this is a very valuable skill I still need to develop it further.

Table 1. Table of achievements

Number of the documents	Medical document
2	Synopsis
2	Clinical Trial Protocol (CTP)
1	Clinical Trial Report (CTR)
2	Manuscripts
2	Systematic review
2	Poster presentation
3	EMWA workshops

5. CONCLUSION

This thesis presents the activities achieved during my training period at Blueclinical, Portugal, as well as all the learning outcomes and skills acquired during this journey.

My internship at Blueclinical as an Associate Medical Writer was my first experience working as a medical writer in a private company. It was very fulfilling as I got the opportunity to acquire knowledge about different types of medical writing activities. I also got the opportunity to get familiarized with other daily activities and organization of the company. Performing the daily activities in the company was a great supplement to the academic training on pharmaceutical medicine and the clinical research that I received from the Masters in Pharmaceutical Biomedicine.

My previous experience in scientific writing and medical communication was enriched with this practical training on medical writing. Even though there were some constraints during my internship, most of them were successfully resolved. During my training at Blueclinical I was mainly focused on regulatory medical writing but since this is very wide and complex, there is still a lot more to learn and explore. Therefore, I am looking forward to continue my learning curve in this area and hopefully to get the possibility to expand my experience in working with other regulatory documents as well.

Throughout my internship I believe I made sufficient progress in my career as a medical writer. In addition, I had opportunities to attend many seminars and workshops organized by the company, which further deepened my knowledge in clinical trials and medical writing. This would not have been possible as an outsider.

As an active member of a European Medical Writing Association, I have the opportunity to stay in touch and get regular updates of new law and regulations in the pharmaceutical industry, which is crucial for performing good medical writing. Also attending the courses at the EMWA Conference in Florence, Italy further sharpened my medical writing skills in new areas.

I believe that the objectives planned for my training internship were fully achieved and accomplished and that I had an opportunity to apply the knowledge from my academic education, which was important for the successful competition of the assigned tasks. I got a better understanding of the clinical research while performing clinical trials, which

tremendously helps to better write the necessary accompanying document, like clinical trial protocols, clinical trial reports, CRF etc.

I can conclude that the Master Degree in Pharmaceutical Biomedicine provided me with a very good background, in particular in the field of the clinical studies and related guidelines and regulations.

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