

# Portuguese Authorship in Published Clinical Trials: Differences in Industry and Investigator Initiated Trials

## Autoria Portuguesa dos Ensaio Clínicos Publicados: Diferenças entre Ensaio Clínicos Iniciados pela Indústria e por Investigadores



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### ABSTRACT

**Introduction:** The aim of this study was to investigate the Portuguese authorship in publications resulting from trials initiated by the industry or investigators and run in Portugal.

**Material and Methods:** Clinical trials with Portuguese institutions as sponsor or recruiting centers, and registered in four clinical trial registries, in the last 14 years, were assessed. Publications of completed trials, from both the initiative of the industry and investigators were screened and compared.

**Results:** The percentage of published trials initiated by industry and investigators was similar (28.0%). However, the percentage of completed investigator-initiated trials (43.6%) was lower when compared to industry trials (69.7%). There was a higher percentage of Portuguese authorship in published investigator-initiated trials when compared with industry-initiated trials (47.1% vs 8.5%, respectively). Moreover, industry-initiated trials with Portuguese authors were published in journals with lower journal impact factor when compared with those published without authorship of Portuguese investigators. Oncology was the therapeutic area with the highest number of clinical trial registrations and publications. However, in publications with Portuguese authors, industry initiated trials mainly focused on neurology while investigator-initiated trials had a higher number of papers in the fields of gastroenterology and infection diseases. Published trials with Portuguese authorship, initiated by the industry or investigators, also targeted different populations and had different purposes. In both cases, no significant differences were observed in terms of the journal impact factor or in the alignment of the published randomized trials with the respective reporting guidelines.

**Discussion:** When compared with previous publications, this study showed an increasing trend in the number of clinical trials in Portugal, published within similar timeframes, after trial conclusion. Even though both industry and investigator trials are published within the standards for reporting trials, the low number of Portuguese authorships in industry publications might underline the need for invigorating these independent clinical trials in Portugal by capacitating and empowering national clinical research teams.

**Conclusion:** This study confirmed that even though all registered trials had the involvement of Portuguese institutions as a recruiting center, not all the published trials had Portuguese investigators as authors, mainly those initiated by the industry.

**Keywords:** Authorship; Clinical Trials as Topic; Portugal; Publishing

### RESUMO

**Introdução:** Este estudo teve por objetivo investigar a autoria Portuguesa em publicações que resultem de ensaios clínicos iniciados pela indústria e por investigadores, que tenham decorrido em Portugal.

**Material e Métodos:** Quatro plataformas de registo de ensaios clínicos foram utilizadas para encontrar ensaios clínicos tendo instituições Portuguesas como promotor ou centro de recrutamento nos últimos 14 anos. Foram analisadas e comparadas as publicações dos estudos completos, da iniciativa da indústria e de investigadores

**Resultados:** A percentagem de ensaios da iniciativa da indústria e de investigadores que são publicados era semelhante (~ 28,0%). Porém, a percentagem de ensaios completos da iniciativa de investigadores era mais baixa (43,6%) quando comparada com os ensaios completos da indústria (69,7%). Existiu uma maior percentagem de autores portugueses em ensaios publicados da iniciativa do investigador quando comparado com os ensaios da iniciativa da indústria (47,1% vs 8,5%). Para além disso, ensaios da iniciativa da indústria com autores portugueses foram publicados em jornais com fatores de impacto inferiores quando comparados com aqueles publicados sem autores portugueses. A oncologia foi a área terapêutica com maior número de ensaios registados e publicados. No entanto, em publicações com autores Portugueses, a indústria focou-se sobretudo na neurologia e os investigadores em gastroenterologia e doenças infecciosas. Ensaio publicados com autores portugueses, iniciados tanto pela indústria como por investigadores, focaram-se em populações diferentes e têm propósitos diferentes. Em ambos os casos, não foram encontradas diferenças estatisticamente significativas no fator de impacto dos jornais, nem no alinhamento dos ensaios aleatorizados publicados com as normas sobre escrita de artigos científicos.

**Discussão:** Quando comparado com publicações anteriores, este estudo mostrou uma tendência de crescimento no número de ensaios clínicos em Portugal, sendo publicados em intervalos de tempo semelhantes após a sua conclusão. Embora os ensaios

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publicados da iniciativa da indústria e de investigadores estejam alinhados com as normas sobre escrita de artigos científicos, o baixo número de autorias nacionais em publicações de ensaios da indústria, sublinha a necessidade de revigorar os ensaios clínicos da iniciativa de investigadores através da capacitação e emancipação das equipas de investigação nacionais.

**Conclusão:** Apesar de todos os ensaios registados terem o envolvimento de instituições portuguesas como centros de recrutamento, nem todos os ensaios têm autores portugueses nas publicações, principalmente aqueles que são iniciados pela indústria.

**Palavras-chave:** Autoria; Ensaios Clínicos como Assunto; Portugal; Publicação

## INTRODUCTION

Clinical studies can be divided into industry-initiated trials (IT), sponsored by pharma/biotech companies, and investigator IT, generally supported by a non-profit organization. The pharmaceutical industry has always been the lead promotor of clinical studies across the world as they lead the technological advances, have the resources to conduct multinational clinical trials and are increasingly using global networks.<sup>1,2</sup> The data gathered in these multinational trials are extremely important because global validation of a treatment efficacy in a broad population is needed to find answers and to continue improving health systems in emerging economies.<sup>1</sup>

Throughout the last decade, the number of investigator ITs has stagnated in most European countries, mainly those involving the use of medicinal products. This is due to the increased burden of laws, regulations and costs, making clinical trials complex, time-consuming and expensive.<sup>3</sup> A study carried out by the Portuguese Clinical Research Infrastructure Network (PtCRIN), shows that for all registered trials from inception to July 2015, the average number of investigator IT per total number of registered clinical trials in Europe is 17.0%.<sup>4</sup> When comparing two countries with a similar population, Portugal and Belgium, the difference in investigator IT number/millions of citizens is 8 vs 67, respectively,<sup>4</sup> with a clear superiority of Belgium over Portugal. In fact, when considering all European countries, only five countries have lower number of investigator IT/millions of citizens when compared to Portugal (Bulgaria, Slovakia, Luxemburg, Poland and Latvia).<sup>1,4</sup>

Despite the lower numbers of investigator IT, when compared to those initiated by the industry, the information provided by those studies is much more important since they generally focus on questions that are not relevant to the industry. Typical examples are therapeutics optimization, comparison of treatments, proof-of-concept studies, orphan disease studies, pediatric trials, among others.<sup>2,5</sup> Above all, these trials provide robust evidence to enable policymakers to make informed and sustainable policy decisions on public health; lead to scientific communications and publications in scientific journals with high journal impact factors (JIF); help building clinical teams, which are the basis for a research center to be considered of excellence.

Usually, in Investigator IT, the clinicians that recruit patients are authors of the publications. On the other hand, in Industry IT, investigators are considered as authors only if they contribute to the protocol design. Moreover, the scope and quality of clinical research from investigator and industry IT may vary. In this sense, we wanted to understand these differences in Portugal.

The objective of this study was to identify the main dif-

ferences between publications resulting from industry and investigator IT with Portuguese institutions as sponsors or/and participating country.

## MATERIAL AND METHODS

The clinical trials included in this analysis were obtained using four online clinical trials registries (CTR): ClinicalTrials.gov, European Clinical Trials Registry (EU-CTR), International Standard Randomized Controlled Trial Number (ISRCTN) registry, and the Australian New Zealand Clinical Trials Registry (ANZCTR). These CTRs encompass 81.0% of the registrations uploaded to the International Clinical Trials Registry Platform (ICTRP) from the World Health Organization (WHO), according to the information provided by others.<sup>6</sup>

The inclusion criteria for trial registrations were: i) clinical trials with medicinal products ii) starting from 1/10/2004 to 30/09/2018 with iii) Portuguese Institutions as sponsor or with Portugal as participating country.

### Search methodology of trials

The search for the medicinal products' clinical trials was performed by two independent authors (MA and DM). In the Clinicaltrials.gov CTR, the three criteria (i - iii) were applied as described above in an advanced search. The EU-CTR only includes medicinal product trial studies, so only two criteria (ii - iii) were applied. In ISRCTN, it was only possible to consider criteria ii) and iii), and therefore observational studies were immediately discarded. In the ANZCTR registry, an advanced search was performed using the three aforementioned criteria needed (i - iii).

Screening for duplicates was performed based on the trial secondary identification number (ID), sponsor name and title of the study, since one trial can be registered in one or more clinical trials registries. This screening was performed independently by two authors (MA and DM). Both authors performed a manual identification of Industry and Investigator IT independently, because clinical trial registries do not have an unequivocal division of the trials in these two categories, with the exception of EU-CTR. This separation was based on the sponsor type. For example, if the sponsor was the pharmaceutical industry then it was considered an industry IT, or in case of a non-profit organization, it was considered an investigator IT. After this separation, the databases of each author were merged, and duplicate trials were immediately excluded. Trials that did not meet the inclusion criteria (e.g. observational trials, trials without medicinal products or trials that do not include Portugal as participating country or sponsor) were also excluded.

### Information about clinical trials

Variables associated with the ID number of the trial, secondary ID, sponsor name, status, start and end date, intervention type, if randomized, title of the study, therapeutic area, were extracted from each database. When a trial was published in more than one database and information was not in agreement between databases, a priority in descending order of the information was given to EU-CTR, ClinicalTrials.gov, then ISRCTN and ANZCTR. The final database with the registrations analyzed in this study is presented as Appendix 1 (Appendix 1: [https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/14554/Appendix\\_01.pdf](https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/14554/Appendix_01.pdf)).

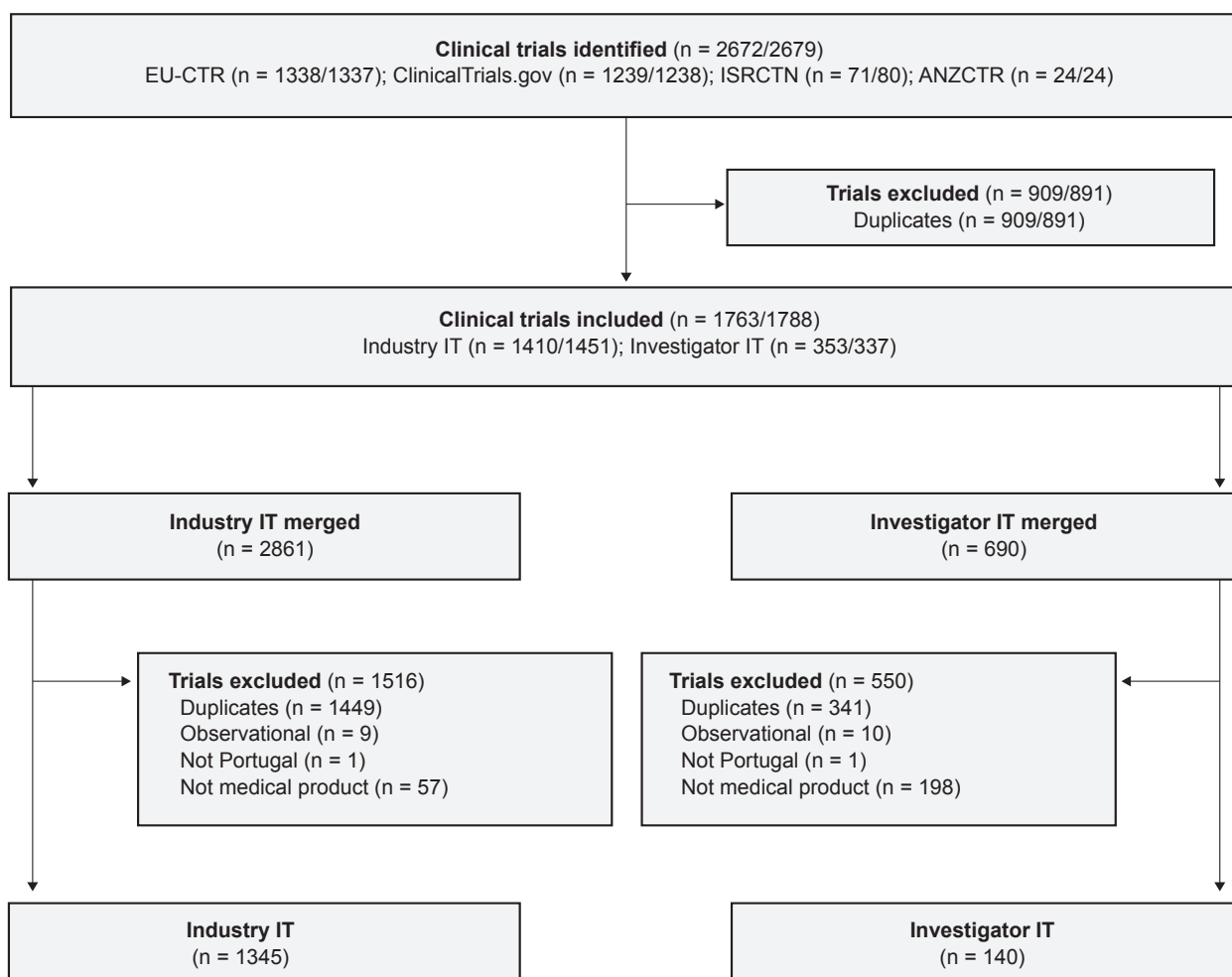
### Identification of publications

PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) was used to identify potential publications resulting from the identified clinical trials. The primary and secondary IDs of completed trials were used to perform this search. Only completed trials, with the trial ID on the abstract were considered and only the first publication with results per trial, published after

trial completion, was included and screened. Details on the completed published trials can be accessed in S.I.1.. Publications of the protocols, comparative studies, publications without the trial ID on the abstract or publication prior to the completion date of the trial were excluded.

### Information about published papers

Information about the date of publication, Portuguese authorship, participating centers, journal name, DOI (digital object identifier), and time from the end of the trial to the publication of results was collected. When the information collected from the clinical trials database was in disagreement with the information provided in the publication, the latter was considered as the correct one. Journal impact factors from the year of the publication were obtained at Web of Science ([www.webofknowledge.com](http://www.webofknowledge.com)). In the publications with Portuguese authorship, information about the purpose (such as treatment with a new product, dose or regimen, prophylaxis, biomarkers evaluation, etc) and the target population was extracted and a screening for compliance with the CONSORT 2010 checklist was carried out



**Figure 1** – Flowchart representing the systematic search in four clinical trial registries of industry and investigator initiated clinical trials with medicinal products, starting from 1/10/2004 to 30/09/2018, and involving Portuguese institutions participating as recruiting center, and/or sponsor.

EU-CTR: European Clinical Trials Registry; ISRCTN: International Standard Randomised Controlled Trial Number; ANZCTR: Australian New Zealand Clinical Trials Registry; IT: initiated trials.

**Table 1** – Number of clinical trial registries and respective percentages, completed, published and those with Portuguese authorship

	Registered trials (nT; %)	Completed trials (nT; %)	Published trials (nT; %)	Portuguese authorship (nT; %)
<b>Industry IT</b>	1345 (1485; 90.6)	938 (1345; 69.7)	271 (938; 28.9)	23 (271; 8.5)
<b>Investigator IT</b>	140 (1485; 9.4)	61 (140; 43.6)	17 (61; 27.9)	8 (17; 47.1)

IT: initiated trials; nT: total number; %: percentage

independently by two authors (MA and CM). This checklist encompasses 25 items that are recommended to follow when reporting randomized clinical trials.

### Statistical analysis

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

For the statistical analysis, data results are presented as mean  $\pm$  standard error or medians and were analyzed with IBM Statistical Package of Social Science version 25.0 (SPSS). Significance analyses were performed for  $p$  values  $< 0.05$  using the Mann-Whitney-U test to evaluate the significance of the difference between two groups of independent samples. None of the samples show a normal distribution, as confirmed by Shapiro Wilk's test. Kaplan-Meier survival plots were used to show the time to publication. The median time to publication and 95% confidence intervals (CI) were calculated.

### Ethics committee approval and consent to participate

Not applicable. No personal information was used in this work. The data used in this work was obtained from public clinical trials databases.

## RESULTS

A total of 2672/2679 registrations were found in the four CTR (ClinicalTrials.gov, EU-CTR, ISRCTN and ANZCTR) by two authors (MA and DM) - Fig. 1. As the same study can be registered in different CTR, several duplicates were found and excluded by each author (909/891) based on the secondary ID, sponsor name and title of the study. Therefore, each of the authors considered at this step 1763/1788 studies, dividing those as industry and investigator-initiated trials.

### Identification of clinical trials

After merging the datasheets prepared by both authors, discrepancies were identified. Non- interventional studies, trials without medicinal products as the intervention or those with no recruiting sites in Portugal were discarded. A total of 1485 trials from the initiative of the industry and of the investigators were considered eligible from all the screened databases (Fig. 1). From those, 1345 (91.0%) are industry IT and 140 (10.0%) were investigator IT (Table 1).

For the screening of publications, only completed trials were considered, identifying a total of 288 publications, 271

(28.9%) publications of industry IT and 17 (27.9%) investigator IT (Table 1). Notably, a considerable higher percentage of investigator IT (47.1%) has Portuguese clinical investigators as authors when compared with those from the industry (8.5%).

### Impact factor of publications and median time to publication

The journal impact factor (JIF) where these trials were published varied widely between 1 to 79. Regarding the median JIF of all these journals, there was a statistically significant difference ( $p < 0.05$ ) when comparing papers with and without Portuguese investigators as authors, since trials with Portuguese authors have a lower median of JIFs (6.1) when compared with those published without Portuguese authors (13.9) (Fig. 2A). Moreover, from all the subgroups presented, published papers with investigator IT was the most variable group (Fig. 2A) whereas papers for Portuguese investigators was the most homogeneous one (Fig. 2A1).

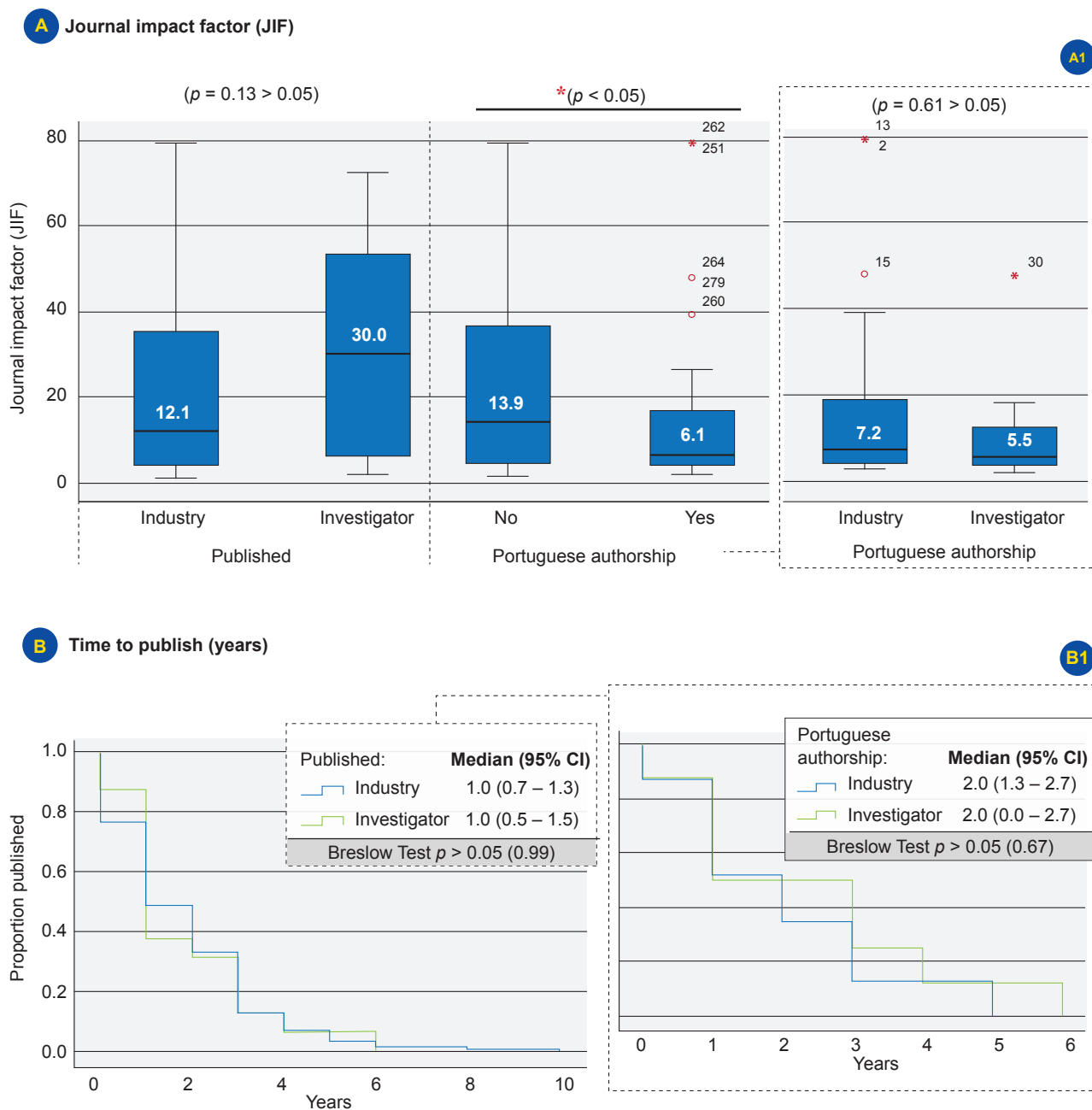
Around 60% of industry and investigator IT were published during the first years after completion of the trial, with no significant differences whether we consider the overall published papers (one year for industry and investigator IT) or the subset of papers published by Portuguese investigators (two years both in industry and investigator IT) (Figs. 2B and 2B1).

### Therapeutic areas of published trials

Oncology was the therapeutic area with the highest number of registrations for both industry and investigator IT (25.7% and 39.3% of trials, respectively). The same is valid for published industry IT ( $n = 58$ ; 21.4%). However, similar numbers of published investigator IT were found in the cardiology/vascular diseases field and infectious diseases when compared with oncology (17.6% each). Regarding Portuguese authorship, a different scenario was found: higher number of neurology trials from the industry initiative were published when compared with oncology (26.1% vs 13.0%), while gastroenterologists and infectious diseases' clinical investigators published a higher number of trials when compared with the other therapeutic areas (25.0% each) (Table 2).

### Published trials with Portuguese authors

The purpose of the published industry IT and investigator IT with Portuguese investigators as authors ( $n = 31$ ) was different. As expected, industry IT explored new prod-



**Figure 2** – Characteristics of clinical trials’ publications, in terms of journal impact factor (A) and time to publish using Kaplan-Meier survival plots (B)

ucts, new indications, new regimens and new doses while investigator IT mainly focused on the comparison of procedures, prophylaxis and biomarker studies (Fig. 3A). The main target population of the investigator and Industry IT were adults (Fig. 3B). Investigator IT also targeted pregnant and pediatric populations while industry IT also focused on older populations (Fig. 3B). Among all these 31 published trials, all the investigator IT were randomized whereas eight industry IT were not randomized (Fig. 3C).

For the analysis of the papers based on the CONSORT checklist, only randomized trials were taken into account (n = 25). Among these randomized trials, no significance differences ( $p > 0.05$ ) were observed between industry and

investigator IT in the average classification of each item in the CONSORT list (Fig. 3D).

**DISCUSSION**

This study compared, for the first-time, industry and investigator IT, specifically analyzing the output in terms of publications and national contribution. The methodology used in this study, allowed us to have a snapshot of trials of medicinal products in Portugal, collecting information from both CTRs and publications.

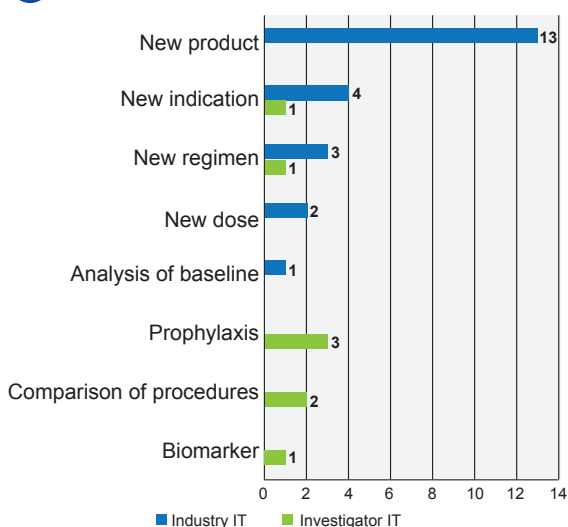
Notably, we found a clear difference in the percentage of trials published with Portuguese authorship, where only 9.0% of published studies initiated by the industry had

**Table 2** – Therapeutic areas of industry and investigator-initiated IT. Subsets for the registered, published and published with Portuguese authors trials.

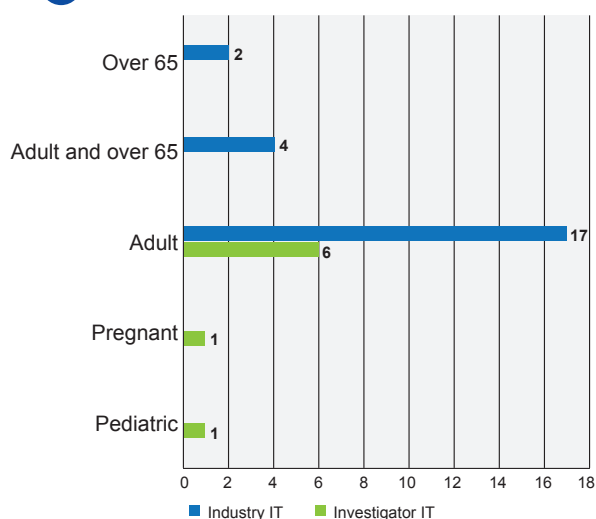
	Industry IT n = 1345	Investigator IT n = 140
<b>Registered clinical trials</b>	Oncology (n = 346; 25.7%) Neurology (n = 146; 10.9%) Infectious Diseases (n = 120; 8.9%)	Oncology (n = 55; 39.3%) Cardiology/Vascular Diseases (n = 19; 13.6%) Musculoskeletal Diseases (n = 9; 6.4%)
<b>Published clinical trials</b>	n = 271 Oncology (n = 58; 21.4%) Cardiology/Vascular Diseases (n = 42; 15.5%) Infectious Diseases (n = 27; 10,0%)	n = 17 Oncology (n = 3; 17.6%) Cardiology/Vascular Diseases (n = 3; 17.6%) Infectious Diseases (n = 3; 17.6%)
<b>Publications with Portuguese authors</b>	n = 23 Neurology (n = 6; 26.1%) Oncology (n = 4; 17.4%) Endocrinology (n = 3; 13.0%)	n = 8 Gastroenterology (n = 2; 25.0%) Infectious Diseases (n = 2; 25.0%) *

\* see Appendix 2 (Appendix 2: [https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/14554/Appendix\\_02.pdf](https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/14554/Appendix_02.pdf))

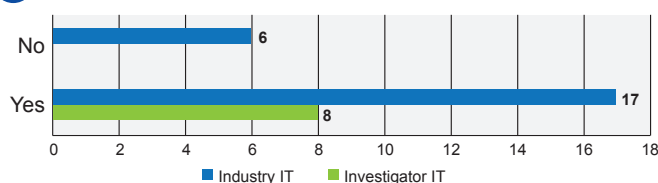
**A Purpose of the clinical trials (n = 31)**



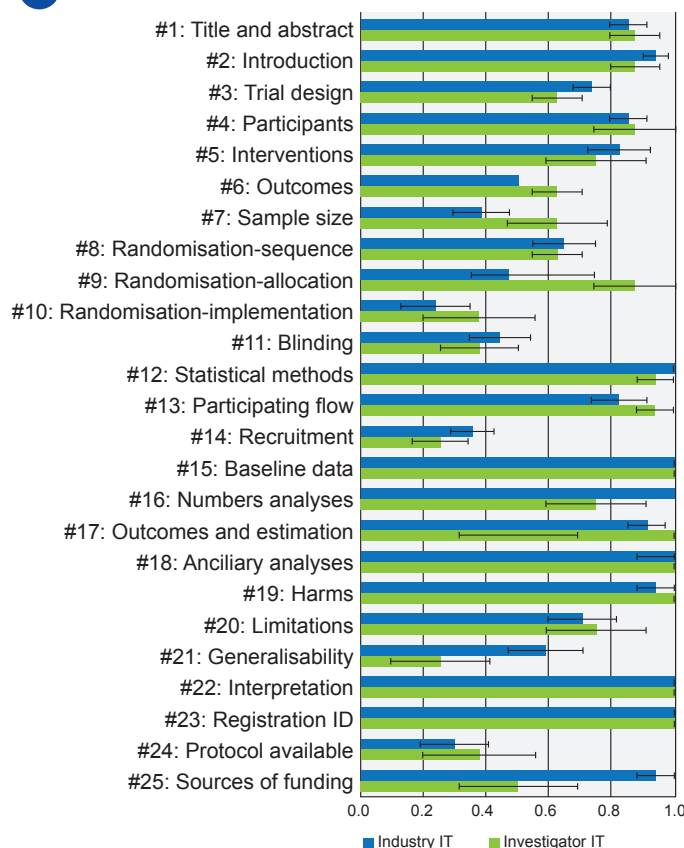
**B Populatin enrolled in the clinical trials (n = 31)**



**C Randomized study (n = 31)**



**D CONSORT checklist analysis (n = 25)**



**Figure 3** – Characteristics of the papers, authored/co-authored by Portuguese clinical investigators in randomized trials. (A) purpose of the clinical trials; (B) type of population enrolled; (C) randomized clinical trials; (D) CONSORT checklist analysis of the randomized papers.

Portuguese clinicians as authors (Table 1). Most probably, in this case, national investigators only participated in the recruitment and not in the design of the study or did not recruit any participant, even though the study was registered in Portugal. The lack of recruitment in international investigator IT might also explain the absence of national investigators in 50% of the published papers. Further investigations, using a different methodology, will follow to confirm if the aforementioned reasons, or others, would be responsible for this discrepancy in the Portuguese authorship of trial publications from the initiative of the industry and investigators.

Most registered trials with Portugal as sponsor or participating country in CTRs were industry IT (90.5%). The numbers are slightly higher when compared with a previously published study in 2016 with Portuguese data,<sup>4</sup> showing the increasing trend in the number of clinical trials in this country. There was a clear difference between the number of registered trials from the initiative of industry and investigators but the percentage of completed trials that were published in both cases is similar (28.9% for industry IT and 27.9% for investigator IT). Indeed, regardless of the source of funding, sponsors may not submit studies with negative findings.<sup>7</sup> However, according to the new EU regulation in clinical research the publication of clinical trials is mandatory. Therefore the aforementioned estimate is expected to increase in the upcoming years.<sup>8</sup> On the other hand, and according to other authors, studies of lower methodological quality are more likely to produce “positive” results and may be more likely to be published.<sup>9</sup> Therefore, it is important to strictly follow international guidelines for study design to ensure a robust level of evidence.<sup>10</sup>

In line with what’s mentioned above, and according to the CONSORT checklist analysis performed in this work, there was no significant difference between industry and investigator IT in any item of the list (Fig. 3D). These findings reveal that, when considering only randomized studies, there is no difference between industry and investigator IT regarding the reporting of the trial. These results agree with the data obtained for JIF showing no significant difference between the published trials with these two types of sponsors ( $p = 0.13 > 0.05$ ; Fig. 2A1) with a clear dispersion of the values in both cases and higher variability in Industry IT. However, Portuguese investigators authored papers published in journals with lower impact factors, when compared with those papers with no Portuguese authors.

Considering the time spent from completion of a clinical trial to the publication of results, most of the trials were published during the first 1 - 2 years for both industry and investigator IT (Figs. 2B and 2B1), considering the median values and Kaplan-Meier analysis. Other authors have reviewed the publication time of results from clinical trials and obtained average values of two years<sup>11</sup> to 5.5 years.<sup>12</sup>

The therapeutic areas both in industry and investigator IT vary whether the study is registered, published or published with Portuguese investigators as authors (Table 2). In fact, within the industry IT, there is a higher number of

published studies with Portuguese authors in the fields of neurology, oncology and endocrinology. Moreover, Portuguese clinical investigators working in gastroenterology and infectious diseases authored a higher number of investigator IT publications, when compared with other therapeutic areas. Nevertheless, oncology is the most studied area in registered and published industry and investigator IT (Table 2). This result is aligned with those obtained by other authors, that did not observe an overall difference in the probability of publication of oncology trials, based on the type of sponsor.<sup>13,14</sup>

Another difference found with this study relates to the purpose and target population of the studies. Industry IT mainly focus on the commercialization of new products or testing new indications, targeting adults and the population over 65 years old. On the other hand, investigator IT use already authorized medicinal products to test prophylactic approaches,<sup>15-17</sup> compare procedures using chemical drugs,<sup>18,19</sup> or discover efficacy biomarkers after using a specific drug for a specific indication (Figs. 3A and 3B).<sup>20</sup> Investigator IT focus on questions not relevant for the industry, and are aimed at providing robust evidence of existing treatments and optimizing the current therapeutics for high-risk populations.<sup>5</sup> In fact, two of the aforementioned studies targeted pregnant women<sup>15</sup> and children.<sup>21</sup>

As a limitation of this study we should point out that the number of trials with medicinal products might be underestimated due to lack of registration and/or misclassification, even though trial registration is mandatory.<sup>22</sup> Moreover, it should be emphasized that in this study, the methodologic approach and inclusion criteria applied for the selection of the publications had to be specific such as: only completed trials and only the first publication with results were considered.

This study underlines the need of Portuguese clinical investigators that actively participate in industry trials to be considered as authors of the subsequent publications. On the other hand, it was shown that both industry and investigator-initiated clinical trials are generally published in journals with high impact factors. For example, investigator-initiated trials, when well conducted, are relevant studies to provide evidence on the best therapeutic option for one specific indication, among others. It is necessary to stimulate these independent clinical trials in Portugal by empowering our clinical research teams. Although clinical trials are complex studies to implement, Portuguese clinical investigators could consider the support of existing initiatives to fund and provide management support to their clinical trials ideas (Agência de Investigação Clínica e Inovação Biomédica (AICIB), European Clinical Research Infrastructure Network (ECRIN) and respective national scientific partner (PtCRIN-Portuguese Clinical Research Infrastructure Network, [www.ptcrin.pt](http://www.ptcrin.pt)).

## CONCLUSION

The proportion of authorship of Portuguese clinical investigators in published investigator IT was higher when

compared with industry IT. Additionally, major differences among published industry and investigator IT, authored by Portuguese investigators, were observed in the therapeutic area, purpose and target population and no significant differences were observed on the reporting quality of the published papers.

#### AUTHORS CONTRIBUTION:

MPA: investigation, data curation, writing original draft preparation

DM: investigation, validation.

JB: methodology, validation, editing.

NG: conceptualization, methodology

HMF: Conceptualization, Validation.

ECM: Validation.

CM: Conceptualization, Methodology, Supervision, Formal analysis, Writing-Review and Editing.

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#### PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

#### DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

#### COMPETING INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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