Investigator-initiated clinical trials conducted by the Portuguese Clinical Research Infrastructure Network (PtCRIN)

C. Madeira a, b, A. Pais a, b, C. Kubiak b, J. Demotes b, E.C. Monteiro a, b, c, *

a Portuguese Clinical Research Infrastructure Network (PtCRIN), Lisbon, Portugal
b European Clinical Research Infrastructure Network (ECRIN), Paris, France

Abstract

Interventional clinical studies can provide the highest levels of evidence and generate significant results on specific investigational medicinal products or medical devices. In order to have powerful studies, attain unquestionable results and make significant discoveries, the number of patients enrolled must be high. Therefore, multinational, randomised clinical trials are necessary. The multicentre, multinational recruitment of subjects in investigator-initiated clinical trials (IICTs) increases their logistical burden, justifying the need for specific infrastructures to ease implementation.

Herein, we provide for the first time an overview of the facts and figures concerning IICTs, existing infrastructures’ capacity for interventional clinical research, and scientific performance of investigators in a European country, Portugal. We aim to highlight the relevance and need for investing in European infrastructures such as the European Clinical Research Infrastructure Network (ECRIN) for multinational IICTs. A public, non-profit organisation, ECRIN facilitates the conduct of multinational clinical trials in Europe by coordinating scientific partners and their networks, and providing advice, management services and tools to enhance collaboration. Currently in Portugal, few multinational randomised IICTs are coordinated by national investigators. This is most likely due to the lack of human resources dedicated to clinical trials in clinical research centres (CRCs) as well as the scarcity of professional academic clinical trial units (CTUs) providing logistics and management services at non-profit rates.

With the data shown, we expect to trigger the development of similar studies in other European countries and stress the impact of government support for IICTs.

© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

The European Clinical Research Infrastructure Network (ECRIN) is one of the pan-European Biomedical and Medical Sciences Research Infrastructures (BMS RIs) listed on the European Strategy Forum on Research Infrastructures (ESFRI) roadmap. It was awarded the status of European Research Infrastructure Consortium (ERIC) by the European Commission in 2013 [1]. ECRIN is a non-profit organisation that strives to harmonise European clinical research; it provides services and coordinates and manages high-quality, independent and fully transparent multinational clinical trials, synergising the capabilities of national clinical research infrastructures. Portugal has signed the ECRIN statutes as a Member Country, together with Germany, Spain, Italy, and France; country membership is paid for by the national government. The Portuguese Clinical Research Infrastructure Network (PtCRIN) is the scientific partner/national hub of ECRIN in Portugal and the other members have homologous infrastructures. Scientific partners aim, on the one hand, to provide support to national investigators seeking to internationalise clinical trials, and, on the other hand, to involve their country in clinical trials initiated by investigators in other European countries. Investigator-initiated clinical trials (IICTs) use a patient-oriented approach and attempt to answer relevant questions in clinical practice that may not otherwise be addressed by companies [2]. IICTs may include studies for possible treatment of rare diseases; paediatric trials with medicinal products authorised for adults; comparative effectiveness trials, enabling the comparison of diagnostic or therapeutic interventions; and simulations of the development of surgical treatments; and simulations of the development of surgical interventions; and simulations of the development of surgical
therapies or novel indications for registered drugs. Above all, IICTs provide the robust evidence to enable policy makers to make informed and sustainable policy decisions on public health. Investigators leading such trials generally obtain financial support from European or national funds, patient associations, other non-profit organisations, or competitive grants from the pharmaceutical industry. A limitation is that these funds are not adapted to the timeframe for patient recruitment and follow-up of chronic diseases, and generally do not allow for subcontracting with for-profit Clinical Research Organisations (CROs). When the logistical support for submission and management of an IICT is lacking, the quality of the research is impaired and investigators face an enormous workload, usually hampering the success of the investigation. Additionally, to extract evidence from an IICT, it is necessary to have a powerful sample, which, in most cases, is only possible to attain in multinational trials. This presents an added challenge without industry sponsorship, as there are different requirements in different European countries. Barriers to multinational IICTs could be reduced by simplifying, centralising, and harmonising application and governance procedures [3,4], and by linking national infrastructures through a distributed network such as ECRIN. For this purpose, the continuous funding and commitment of governments is crucial.

The present study aims to analyse the current status of IICTs in one ECRIN Member Country, i.e., Portugal. Results were gathered from members of the scientific partner (PtCRIN). For the first time, we provide quantitative indicators on IICTs that might be useful for restructuring priorities towards strengthening competitiveness in different European countries.

2. Methods

2.1. PtCRIN members

PtCRIN includes eight healthcare units (Centro Hospitalar da Cova da Beira — CHCB; Centro Hospitalar Lisboa Central — CHLC; Centro Hospitalar de Lisboa Ocidental — CHLO; Centro Hospitalar do Porto — CHP; Centro Hospitalar São João — CHSJ; HFF — Hospital Prof. Doutor Fernando da Fonseca; Instituto Português de Oncologia de Lisboa — IPO-L; Instituto Português de Oncologia do Porto — IPO-P), one non-profit clinical research organisation (Association for Innovation and Biomedical Research on Light, AIBILI), and five academic medical centres or universities (Centro Clínico Académico de Braga — 2CA-Braga; Centro de Investigação Clínica - Centro Académico de Medicina de Lisboa — CIC-CAML; Faculdade de Medicina da Universidade do Porto — UC; Instituto Nacional de Investigação e Desenvolvimento em Saúde — IPO-P; Nova Medical School, Universidade Nova de Lisboa — NMS; University of Coimbra — UM). The selection of PtCRIN members was determined based on a survey sent in 2013 to all health organisations in Portugal with ongoing clinical trials, aiming to assess capacity for clinical research. Organisations with the highest number of clinical trials, affiliated with medical schools, and motivated to improve their clinical research units and to internationalise their performance in clinical research were retained. Later, end 2014, another survey was sent to all 14 PtCRIN members to receive updated information on their capacity in terms of clinical trials and respective facilities. From April to July 2015, a meeting was held between the representatives of each member institution and the PtCRIN core team; this was the opportunity to confirm member expectations regarding PtCRIN, as well as their capacity, facilities, employee data, and number of IICTs.

Under the ECRIN framework, PtCRIN members are divided according to the following categories [5]:

a) Clinical Research Centres (CRCs), health care-based organisations devoted to clinical research, with designated beds, equipment, medical and study-nurse staff, allowing enrolment and investigation of patients in the early phases of drug trials and in non-therapeutic studies (CHP, CHSJ, CHLC, CIC-CAML, IPO-L, IPO-P, CHCB, 2CA-Braga, AIBILI).

b) Clinical Trial Units (CTUs) to manage clinical trials, namely randomised clinical trials (phase II-IV), prognostic, diagnostic studies, and meta-analyses, dealing with the design of the study, its organisation, logistics, centre selection, data management, monitoring, data analysis, pharmacoepidemiology, and reporting (NMS, AIBILI, and to be developed by UC and FMUP).

2.2. Number of clinical trials in European countries

Clinical trial data for this study were obtained from the European Clinical Trials Database (EudraCT, www.clinicaltrialregister.eu) using the search terms/status “name of the country” and “commercial/non-commercial”; the search was limited to the period prior to 31 July 2015. The number of citizens was obtained from Eurostat (http://ec.europa.eu/eurostat) in July 2015.

2.3. Number of and details on clinical trials initiated by investigators in Portugal

Data were obtained from the EudraCT database in July 2015 using the search terms “Portugal” and “non-commercial”. Only ongoing clinical trials in Portugal that were clearly initiated by investigators were considered. A total of 51 clinical trials were found (S.I.1). The distribution of ongoing clinical trials in each institution

| Abbreviations | Description |
|---------------|-------------|
| IICTs | Investigator-Initiated Clinical Trials |
| 2CA | Clinical Academic Center — Braga [Centro Clínico Académico de Braga] |
| AIBILI | Association for Innovation and Biomedical Research on Light and Image [Associação Para a Investigação Biomédica e Inovação Em Luz e Imagem] |
| CEIC | Portuguese National Ethical Commission [Comissão de Ética para a Investigação Clínica] |
| CHCB | Centro Hospitalar da Cova da Beira |
| CHLC | Centro Hospitalar Lisboa Central, E.P.E. |
| CHLN | Centro Hospitalar de Lisboa Norte, E.P.E. |
| CHLO | Centro Hospitalar de Lisboa Ocidental, E.P.E. |
| CHP | Centro Hospitalar do Porto, E.P.E. |
| CHSJ | Centro Hospitalar São João, E.P.E. |
| CHUC | Centro Hospitalar da Universidade de Coimbra |
| CIC-CAML | Centro de Investigação Clínica - Centro Académico de Medicina de Lisboa |
| FMUP | Medical School from Oporto University [Faculdade de Medicina da Universidade do Porto] |
| FTE | Full Time Equivalent |
| IPO-L | Oncology Institute of Lisbon [Instituto Português de Oncologia de Lisboa] |
| HFF | Hospital Prof. Doutor Fernando da Fonseca |
| IPO-P | Oncology Institute of Oporto [Instituto Português de Oncologia do Porto] |
| NMS | Nova Medical School [Faculdade de Ciências Médicas], Universidade Nova de Lisboa |
| UC | University of Coimbra [Universidade de Coimbra] |
| UM | University of Minho [Universidade do Minho] |
was kindly provided by the national Ethical Commission (Comissão de Ética para a Investigação Clínica, CEIC) for registries submitted between 2011 and still ongoing as of July 2015.

2.4. Number of and details on investigator-initiated interventional studies in Portugal

Data were obtained from the clinicaltrials.gov database in July 2015 using the terms “Portugal”, “device” or “procedure”. Only ongoing, interventional studies with known status were considered. Of the 53 studies screened, only 19 did not have industry sponsorship (S.I.2).

2.5. Number of publications about clinical research in Portugal

All studies published in English or Portuguese addressing interventional studies in Portugal were identified. This was achieved by searching the PubMed MEDLINE database, first using the term “Randomi*” in the title, and “Portugal” in the address from January 2010 to August 2015, and then using the name of the health centre, and “Portugal” in the address from January 2014 until August 2015. With the first search, 209 publications were found and screened; only 48 focused on randomised interventional studies with drugs or medical devices (S.I.3) and were considered for this publication. Feedback to validate this information was requested to all PtCRIN members: responses were provided from 2CA-Braga, AIBILL, CHCB, CHLC, ChHP, IPO-L and IPO-P.

After registering data from the latter search, a table was sent to each PtCRIN member to confirm the number and details of the publications and to request missing information. Responses were provided from 2CA-Braga, AIBILL, CHCB, CHLC, ChHP, IPO-L and IPO-P. A total of 1540 publications were screened.

3. Results

3.1. Clinical trials in Europe: commercial vs. investigator-initiated clinical trials

European countries such as the United Kingdom (UK), Italy, Germany and Spain were able to attract industry sponsorship for clinical trials (>4000 clinical trials registered until July 2015), enabling access to innovative medicines for patients and stimulating high-quality clinical research (Fig. 1A). In Europe these countries also have the highest number of IICTs (>1500), representing only 20–35% of the total number of registered trials in each country (Fig. 1A, S.I.4). In Portugal, only 8% of all registered clinical trials are initiated by investigators without industry sponsorship, while the European average is 17% (Fig. 1A). Indeed, Portugal is below the European average in regards to both types of clinical trials. When considering the size of the population in each country, Denmark, Austria and Finland are the ones with the highest number of clinical trials per one million citizens (Fig. 1B).

3.2. Investigator-initiated interventional studies in PtCRIN member institutions

From the 917 interventional studies (drugs, medical devices and surgical procedures) ongoing in Portugal, 70 are non-commercial, corresponding to 8% of the total number of clinical trials (Fig. 2A). Interestingly, only 13% (n = 9) of these investigator-initiated studies are non-randomised (Fig. 2B) and most studies involve the use of chemical drugs (Fig. 2C) in Phase III (Fig. 2D). Around 64% (n = 45) of IICTs ongoing in Portugal are multinational (Fig. 2E), which shows the openness of Portuguese investigators to embrace international studies. Additionally, investigators from CHLN, AIBILL and CHSJ are sponsors of international studies (S.I.11).

As expected, most of the clinical trials currently being conducted by PtCRIN members are industry-initiated. At oncology institutes, IPO-P and IPO-L, and CHLO, more than 10% of the total number of clinical trials are initiated by investigators (Fig. 3A). It is noteworthy that the percentage of IICTs at IPO-L, around 30%, is similar to that observed in European countries with the highest number of IICTs (Fig. 1B). Another relevant fact is that 64% of the total number of IICTs in Portugal are multinational and the majority are focused on cancer, followed by heart and joint diseases (Fig. 3B).

3.3. Human resources allocated to clinical trials in PtCRIN members

At the moment, PtCRIN is a consortium of institutions and is focused on developing two major activities: i) establishing and developing a coherent national network of CTUs compliant with European and national guidelines and regulations; and ii) developing national CRCs with the minimum requirements needed to perform clinical trials compliant with national and European regulations/guidelines. Currently, PtCRIN has two CTUs providing external services at non-profit rates for the management of clinical trials, including those that are multinational.

As shown in Fig. 4, large hospital centres (number of beds > 1000) (CHLO, CHLC, CHP, CHSJ, CHCB, 2CA) and oncology institutes (IPO-L, IPO-P), public non-profit organisations, are currently struggling with the lack of human resources exclusively allocated to clinical trials. Even IPOs, with a higher percentage of IICTs and huge potential for starting IICTs, have relatively few dedicated resources (S.I.5). Nonetheless, several hospitals in Portugal have already begun centralising clinical research unit procedures, quality management systems and publications in peer-reviewed scientific journals.

3.4. PtCRIN member publications in clinical research

The results gathered in this section include all types of publications, namely: randomised studies, systematic reviews and meta-analyses, non-randomised interventional and observational studies, and case reports. From January 2014 until August 2015, PtCRIN members collectively published around 2,5 of such papers every day. Fig. 5 includes a summary of information collected from 1540 publications by PtCRIN members published in this timeframe. Based on the information amassed from the last 20 months and depicted in Fig. 5, it is clear that most of the studies are accomplished solely by national teams and published in journals with an impact factor (i.e., index that reflects the number of citations) between 1 and 4. The physicians from the therapeutic areas of oncology, cardiology, neurology and gastroenterology have higher publication rates when compared to other areas of medical expertise. In Fig. 5D, it is possible to observe that high numbers of IICTs in Portugal are multinational and the majority are focused on cancer, followed by heart and joint diseases (Fig. 3B).
investigators had the same level of support for their ideas as industry studies receive, they would also be able to accomplish randomised, complex clinical trials and publish their findings in high-impact scientific journals.

4. Discussion

Randomised screening trials are bothersome. It takes ages to come to an answer, and these need to be large — scale projects to be able to answer the questions. [But …] there is no second-best option.

H.J. de Koning, Annals of Oncology, 2003

To the best of our knowledge, this is the first study specifically addressing the performance of a country in terms of investigator-initiated clinical studies. Comparison with other European countries is difficult because indicators of scientific performance, human resources allocated to clinical trials or therapeutic areas of non-commercial clinical trials are not commonly explored in available publications. We intend to highlight the relevance of using performance indicators in clinical research as well as to underline the advantages of country membership in ECRIN as a means to facilitate multinational IICTs.

Throughout the last decade, the adoption of directive 2001/20/EC by each European country led to a clear decrease in the number of academic trials [2]. Indeed, investigators carrying out a study with a well-established drug that is commonly used in daily practice have to comply with the same rigorous regulations as large pharmaceutical companies investigating the potential of a novel therapy; this applies even though, in most cases, the risk for the trial participants does not always justify the financial and regulatory burdens imposed [6]. Besides regulatory fragmentation in different countries, there are other bottlenecks in the conduct of multinational studies including informed consent, ethical review, data monitoring, adverse events, insurance, costs, funding, training and language [7]. In Europe, the number of applications to undertake clinical trials fell from 5000 to 3800 between 2007 and 2011, and the administrative costs for academic trials rose by 98% [8]. On the other hand, in Denmark an opposite trend was observed; this can likely be explained by the implementation in 1999 of good clinical practice units in universities and hospitals, with public funds, to support the implementation and management of IICTs [9]. Denmark is currently the country with highest number of clinical trials per one million citizens (Fig. 1B).

In Germany, in a successful attempt to circumvent the aforesaid problems, a former working group of the Coordinating Centres for Clinical Trials was transformed into a consortium supported by the government — the KKS Network [10,6]. From 1999 to 2015, the KKS Network received 77 million euros from the German government. The existence of this infrastructure of clinical trial units (CTUs) might be responsible for the highest values of clinical trials per million citizens, including IICTs when compared to other European countries (Fig. 1B). The French government provided total funding of 18 million euros for a period of eight years to create FCRIN (www.fcrin.org), which is the French scientific partner of ECRIN. In France, investigators have access to several types of training, including H2020 training for clinical trials; they are supported by a strong network of CTUs and CRCs; and they are extremely competitive in attracting European funds. In the UK, a registration process was developed to ensure that CTUs meet regulatory and quality standards (www.nets.nihr.ac.uk/programmes/c tu). With this multi-stage, government-supported activity, the number of cancer patients enrolled in clinical trials increased by 20% [11]. Besides providing operational support to manage interventional studies initiated by investigators or thematic networks, these CTUs can also contribute to establishing a harmonised quality management...
system for these activities at national and/or international level and provide training in good clinical practices (GCPs).

Based on these examples, the involvement of local and distributed (i.e., spanning across different countries) infrastructures to support investigators throughout the entire process of a clinical study seems crucial to fulfill the requirements and achieve the objectives in IICTs. As such, the involvement of ECRIN, a distributed network, and PtCRIN, a national network encompassing multiple Portuguese partners, is a step in the right direction.

Currently in Portugal, the percentage of IICTs is still below average when compared to all countries in the European Union (Fig. 1). The reasons are mainly related to: a) the low number of national programmes for non-commercial clinical research funding (the few programmes that are launched are insufficient for sponsoring powerful interventional clinical studies); b) limited funding for PtCRIN core activities; c) insufficient human resources, including physicians, fully dedicated to clinical trials in health centres; and d) lack of local infrastructures such as CTUs to support investigators in non-commercial trials.

Most ongoing IICTs in Portugal are randomised and are sponsored by non-for-profit organisations with national and/or European funds. Additionally, around 64% of the IICT in Portugal are multinational in agreement with the results recently shown by others [12]. This number shows that the first steps towards increasing the number and impact of these clinical trials have been taken. Oncology institutions have a higher percentage of IICTs when compared to other national health organisations (Fig. 3A). Nevertheless, they are struggling with the need for human resources fully dedicated to clinical trial operations (Fig. 4). The main consequence of this is a slow recruitment of patients and lower capacity for accepting new clinical trials, even from the industry. Indeed, the feasibility of randomised trials often depends on successful patient recruitment [13]. A recent study (SAT-EU) systematically investigated factors impacting trial site attractiveness across Europe; it found that investigator-dependent factors, such as recruitment speed and ease of approval, dominate trial site

---

**Fig. 2.** Percentage of ongoing, interventional clinical studies (IICT) in Portugal (Total number = 917). A) Type of sponsor; B) Design of the non-commercial study that includes IICTs on medical devices and surgical procedures; C) Type of health technology of non-commercial clinical studies; D) Development phase of non-commercial medicine; E) Location of non-commercial clinical studies.
selection, while costs appear less important [14]. The above-mentioned KKS Network in Germany is one successful example of an organisation that has been able to increase recruitment efficacy [15].

In line with what is observed in other countries, oncology is the largest therapeutic area in ICTs and most ICTs in this field are multinational, although few sites are generally considered to recruit patients (S.I.1). Additionally, a small number of ICTs have a national sponsor, clearly reflecting the lack of capacity of organisations to incite investigators to lead multinational studies, especially those funded by European initiatives.

Despite the high percentage of randomised trials when compared to the total ICTs in Portugal (Fig. 2B, E), the former represents only around 2% of all published papers since 2014.
Indeed, the accomplishments of IICTs are generally published in peer-reviewed scientific papers or presented in conferences, which are increasingly valued as a means to attract further funding and to boost an investigator’s career. Additionally, since October 2013, the World Medical Association (WMA) Declaration of Helsinki included the mandatory requirement of making publicly available the results of research on human subjects, including negative results independently of the type of sponsor [16].

The majority of our publications in clinical research rely on the description of case reports (30%) and observational studies (25%) with an average impact factor of 2.5 and 3, respectively (Fig. 5D). Conversely, randomised studies are published in journals with an average impact factor of 7. The design, implementation, conduct and results analysis of these studies should be performed in a structured way to increase the power of the evidence of the results [17]. Therefore, the existence of national and international clinical research infrastructures with experts to support physicians in these clinical trials is decisive.

In Europe, countries with these infrastructures, such as Germany, France or the UK have shown a rise in the number and quality of clinical trials. ECRIN scientific partners such as PtCRIN have a key role in this process; they bring together national infrastructures in clinical research, linking national investigators to a European infrastructure (i.e., ECRIN) of patient recruitment sites and CTUs for managing clinical trials locally. Although the assessment of the impact of being integrated in this consortium will be evident in the near future, current progress probably would not have been achieved without the involvement of ECRIN.

Overall, this work attempts to create a precedent in European countries to evaluate the added value of ECRIN and to measure the impact of investigator-initiated clinical research in the healthcare sector. It suggests some indicators that might be considered; other

---

**Fig. 5. Scientific papers of PtCRIN members published in peer-reviewed journals cited in PubMed between January 2014 and August 2015 (in percentage; total = 1540).**

- **A** Type of teams involved in published papers involving international cooperation
- **B** Impact factor (IF) range for journals in which scientific papers were published
- **C** Percentage of papers published with work regarding each area of medical expertise
- **D** Overlay of the graph displaying the number of publications (%) using each study type with the graph showing the average IF (green) of the journals where the paper was published - calculated as the ratio between the accumulated IF (Accum. IF) and the number of papers published for each study type. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

---

**Fig. 6. Randomised clinical studies accomplished in Portugal and published from 2010 to July 2015 (Total number = 48).**

- **A** Percentage of different health technologies used in the published studies
- **B** Number of investigator- and industry-initiated clinical trials and medical device studies carried out in Portugal alone (national) and in several countries (multinational).
quantitative indicators such as recruitment efficacy and speed are expected to be included in future analysis.

5. Conclusions

The first steps towards high-quality IICFs in Portugal have been taken through membership in ECRIN. Although PtCRIN’s scientific output is far from the desired result, we foresee that being a scientific partner of ECRIN will increase performance in the next few years. Our results might trigger the development of similar studies in other European countries seeking to confirm ECRIN’s added value and produce accurate comparative studies in IICFs. The engagement of national governments in building the capacity of infrastructures dedicated to managing interventional IICFs at non-profit rates is, in our view, crucial to achieve high-quality evidence in health technologies to improve health care and the sustainability of health systems.

Conflict of interest statement

None.

Contributors

AP and EM conducted the survey with the representative of each PtCRIN member and AP and CM conducted the face-to-face interviews. CM performed the clinical trials and publications search, screening and results analyses. All authors contributed to the preparation and review of the manuscript.

Acknowledgements

We would like to acknowledge the kindness of Prof. Alexandra Ribeiro and availability of Dr. Filipa Oliveira and Dr. Raquel Silva from Comissão de Ética para a Investigação Clínica (CEIC) for providing the name of the research sites for each ongoing investigator-initiated clinical trial registered in Portugal and also the number of clinical trials per institution. We also want to acknowledge all representatives of PtCRIN member for the information provided in the survey and interviews. The authors also want to acknowledge Sabrina Gaber for the professional editing of this manuscript. The work of CM and AP is being supported by Fundação para a Ciência e a Tecnologia (FCT, through the membership fees to ECRIN-ERIC published at Portaria n.° 237/2014).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.conctc.2016.08.002.

References

[1] A. Calzolari, A. Valerio, F. Capone, M. Napolitano, M. Villa, F. Picci, E. Bravo, F. Belardelli. The European research infrastructures of the ESFRI roadmap in biological and medical Sciences: status and perspectives, Ann. Ist. Super. Sanita 50 (2014) 2–178.
[2] A.D. McMahon, I. David, D.J. Conway, T.M. MacDonald, G.T. McInnes, The unintended consequences of clinical trials regulations, Plos Med. 6 (2009) 11–e1000131.
[3] E. Berge, G.A. Ford, P.M.W. Bath, C. Stapf, Worp HBvd, J. Demotes, Salmon RA-S. Broderick, R.K. Lees, Regulation and governance of multinational drug trials in stroke: barriers and possibilities, Int. J. Stroke 10 (2015) 3–425.
[4] A. den Exter, European Commission updates rules on clinical trials, Contemp. Clin. Trials (2013) 34–173.
[5] G.H. Guyatt, D.L. Sackett, J.C. Sinclair, R. Hayward, D.J. Cook, R.J. Cook, E. Bass, H. Gerstein, B. Haynes, A. Holbrook, R. Jaeschke, A. Laupacis, V. Moyer, M. Wilson, Users’ guides to the medical literature- a method for grading health care recommendations, JAMA 274 (1995) 22–1800.
[6] H. Maier-Lenz, Academic strength in Germany, Appl. Clin. Trials (2011). http://www.appliiedclinicaltrialsolution.com/academic-strength-germany/?id=&sk=&date=&pageID=5.
[7] J. Demotes, C. Ohmann, European clinical research infrastructures network: promoting harmonisation and quality in European clinical research, Lancet 365 (2005), 9454–107.
[8] F. Yaqub, SIOPE proposes amendments for EU clinical trials regulations, Lancet Oncol. 14 (2013) 4–282.
[9] L. Berendt, C. Hakansson, K.F. Bach, K. Dalhoff, P.B. Andreasen, L.G. Petersen, E. Andersen, H.E. Poulsen, Effect of European clinical trials directive on academic drug trials in Denmark: retrospective study of applications to the danish medicines agency, 1993-2006, BMJ 336 (2003), 7634–33.
[10] E. McFadden, S. Bashir, S. Canham, J. Darbyshire, P. Davidson, S. Day, S. Emery, J. Pater, S. Rudkin, M. Stead, J. Brown, The impact of registration of clinical trials units: the UK experience, Clin. Trials 12 (2015) 2–166.
[11] T. Atal, L. Trinquart, R. Porcher, P. Ravaud, Differential globalization of industry- and non-industry-sponsored clinical trials, PlosOne 10 (2015) 12.
[12] A. Spaar, M. Frey, A. Turk, W. Karzer, M.A. Puhlan, Recruitment barriers in a randomized controlled trial from the physicians’ perspective – a postal survey, BMC Med. Res. Methodol. 9 (2009) 14.
[13] G.H. Guyatt, D.L. Sackett, J.C. Sinclair, R. Hayward, D.J. Cook, R.J. Cook, E. Bass, H. Gerstein, B. Haynes, A. Holbrook, R. Jaeschke, A. Laupacis, V. Moyer, M. Mark Wilson, Users’ guides to the medical literature IX. A method for grading health care recommendations, JAMA 274 (1995) 22–1800.
[14] D. Delawi, W.J.A. Dheert, F.C. Oner, Conducting a European multi-center trial: first experiences with the new EU Clinical Trials Directive from an academic perspective, Eur. Spine J. (2008) 171–1113.
[15] World medical association declaration of Helsinki. Ethical principles for medical research involving human subjects, JAMA 310 (2013) 20–2191.
[16] W. Pearce, S. Raman, A. Turner, Randomised trials in context: practical problems and social aspects of evidence-based medicine and policy, Trials (2015) 16–394.