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An EU comparative analysis of the regulation of clinical trials supervisory bodies in the aftermath of Regulation 536/2014

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Key words: ethics committees, clinical trials, Regulation on clinical trials, regulatory competition

Abstract

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The new EU regulation on clinical trials is intended to promote a greater level of harmonization of European Union rules in this area. However, it does not elaborate a common normative framework regarding the functioning of research ethics committees, leaving this responsibility to the Member States. This article offers a comparative analysis of the resulting regulatory situation. It demonstrates that this scenario is defined by considerable variability in the regulation of ethics monitoring between the EU Member States. We argue that this disparity should not necessarily be a negative factor for the optimization of the trial supervision regime in the EU. Moreover, we consider that it may be a stimulus for the achievement of excellence in the performance of this monitoring task. On the other hand, we also highlight risks for the rights of participants if an adequate monitoring framework is not ensured. Under these circumstances, we observe how the EU faces a dilemma. On the one hand, it may promote a rigid uniformity between the regulation of ethics committees between Member States, but this might diminish the quality of their performance. On the other hand, it may opt for maintaining the current situation, but this might increase differences in the performance of the ethics committees between Member States, including the number trials performed by country. A third option would be to allow the competitive framework to remain for a set period of time, in order to learn from the best practices reached in individual Member States before finally harmonizing national legislative provisions on this basis.

1. Introduction

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC entered into force on 16 June 2014.[1] This new Regulation aims to foster innovation and research, stimulating quick access to new, innovative treatments and ensuring that the EU remains an attractive place for conducting clinical trials[2]. To this end, it is intended to result in a greater level of harmonization of the rules on clinical trials throughout the EU. In theory, this will make it easier for pharmaceutical companies to conduct the necessary trials and, consequentially, should increase the number of studies conducted within the EU. However, in spite of such moves towards regulatory harmonization, some essential aspects have been left to the jurisdiction of the Member States. The regulation of the ethics committees involved in clinical trials constitutes a paradigmatic example of this, since the supervision of ethical issues regarding clinical trials will remain in the hands of ethics committees appointed on the basis of, and regulated by, Member States' national legislation.[3] According to the European Medicines Agency website, the audit of the system will commence in December 2020.[4]

At first sight, one may think that this situation does not work well with the goal of harmonizing the EU legal framework on clinical trials. However, we believe that the existence of alternative regulation in the EU area can be a positive factor in improving the functioning of clinical trials in the long term. Moreover, it could also create a stimulus for the eventual convergence of best practices built on the experiences gained from this regulatory fragmentation. We suggest that the freedom given by the EU area to Member States to regulate the organization and functioning of their own ethics committees (monitoring the clinical trials) creates a situation of regulatory competition[5] among countries, and sometimes even among committees themselves. We anticipate that this will

[1] Its application, however, will be delayed until the European Commission announces that an independent audit confirms that a fully functional EU clinical trials portal and database has been developed. To be more precise, the Regulation will become applicable six months after the publication of the notice of this confirmation.
[2] See (8) of the Regulation.
[3] See (18) of the Regulation.
[4] See: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation [accessed 18 April 2020]
[5] I. De Miguel Beriain, '¿El Derecho, moneda de cambio? "Regulatory competition" en la era de la globalización' (2007), *Revista de Derecho UNED*, Nº2,121-143,

likely improve the overall process of the evaluation and approval of clinical trials in the EU context.

This hypothesis is strengthened to the degree that the efficiency of the ethical supervisory body is a key factor to determine the attractiveness of a particular Member State or research centre for a sponsor. Available data[6] suggests that predictability and speed of ethics committees and institutional review boards (IRBs) for phase II–III multi-centre randomised controlled trials (RCTs) constitutes one of the main reasons why sponsors choose a particular location to conduct trials instead of another. Conversely, the existence of multiple ethics committees with different sets of requirements leading to overly complex multiple trial contracts would seem less attractive. Moreover, the lack of well-educated ethics committees that may delay approval and regulatory assessments (e.g. by unreasonably requiring excessive explanatory details in the protocol and during participant enrolment) have been shown to hinder the development of clinical trials[7]. Therefore, if promotors are empowered to choose the country or even committee that supervises their trials, they will probably opt for the more efficient ones. If this is the case, the fragmented regulatory framework may tend to gradually create a convergent situation in terms of best practices in the long term.

This article will develop these hypotheses by first showing the significant differences in the organization, allocation of the supervision and financial resources assigned to the committees in individual EU Member States. We then argue that such a complex scenario may serve as a valuable tool to analyze situations that may subsequently arise and to make some considerations on its final performance in terms of the harmonization of ethics committee practices at the EU level. To this end, we perform a comparative analysis that covers several EU Member States, including Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Portugal, Spain and Sweden. These have been chosen for a number of reasons, such as their population, cultural tradition, as well as the particularities of their current regulation on clinical trials. Together, they form a sample ideally tailored to probe the shape of the regulatory landscape in the EU ahead of the implementation of the new legal framework.

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[6] M. Gehring, R.S. Taylor, M. Mellody, et al 'Factors influencing clinical trial site selection in Europe: the Survey of Attitudes towards Trial sites in Europe (the SAT-EU Study)', (2013), *BMJ Open*. doi: 10.1136/bmjopen-2013-002957.

[7] R. Hernandez, M. Cooney, C. Duale et al. 'Harmonisation of ethics committees' practice in 10 European countries' (2009) *J Med Ethics*. 35(11), 696–700. Epub 2009/11/03; E. A. M. Neugebauer, A. Rath, S. L. Antoine, et al. 'Specific barriers to the conduct of randomised clinical trials on medical devices' (2017) *Trials* 18, 427.

2.- Organization of the Ethics Committees. Accreditation, monitoring and control

The organization of clinical trial ethics committees varies considerably in the selected countries, according to variables such as their accreditation or the monitoring and control tools designed to ensure their adequate performance. In Belgium, the new regulatory framework[8] has established a new independent body, known as '*The College'* which coordinates the functioning of ethics committees and is responsible for monitoring their quality, particularly with the establishment of a new accreditation system. Every hospital currently having an ethics committee or aiming to install one in the future will have to undergo the new accreditation procedure with the Federal Agency for Medicines and Health Products (FAMHP or FAGG in Dutch). Consequently, existing ethics committees will also be obliged to file a new application to be accredited. The accreditation is allocated by the Federal Agency for Medicines and Health Products and must be renewed every four years. Although the FAMHP ensures the allocation of the ethics committees, it is not responsible for the monitoring of its quality. Instead, the law of 7 May of 2017 assigned this task to the College (Art. 9). It will guard over the quality of the ethics committees by means of recommendations and feedback. These results can subsequently be taken into consideration by the FAMHP when the hospital files an accreditation request (Wet klinische proeven, 2017).

In Denmark, regional ethics committees are set up by the regional councils on a geographic basis based on the recommendation of relevant research based-forums. The members are appointed every four years (timed to correspond with applicable regional elections) and may be reappointed twice (§35 and 36(5) Executive Order no. 1083). According to Act no. 620, the Minister for Health and Public Affairs may lay down further

[8] Wet betreffende klinische proeven met geneesmiddelen voor menselijk gebruik. (May 7th, 2017). Retrieved from https://www.ejustice.just.fgov.be/mopdf/2017/05/22_1.pdf#Page21; Koninklijk besluit tot uitvoering van de wet van 7 mei 2017 betreffende klinische proeven met geneesmiddelen voor menselijk gebruik. (Oct 9th, 2017). Retrieved from http://www.ejustice.just.fgov.be/mopdf/2017/11/10_1.pdf#Page56; Wet inzake experimenten op de menselijke persoon. (May 7th, 2004). Retrieved from https://www.ejustice.just.fgov.be/mopdf/2004/05/18_2.pdf#Page2 [accessed 27 April 2020].

rules on requirements for documentation (as proof) that the members of the scientific ethics committees do not have any conflicts of interest and that they are independent of the sponsor, the location of the clinical trial, the investigators involved and those who finance the clinical trial, and that they are not under any other undue influence (§7(11)). Moreover, the ethics committees are required to supply an annual report containing a statement of their activities and practices from the past year (§34, Executive Order no. 1083).

In France, the *Comités de Protection des Personnes* (hereinafter CPP) are accredited by the Ministry of Health on the proposal of the General Director of the regional agency for health of the related region. Their members are appointed by the General Director of the Regional Agency for Health of the Region in which the CPP has its seat (Article L1123-1 Code de la Santé Publique Français (CSP)). The accreditation is delivered for six years and the renewal follows the same model, being processed and delivered in the same way (Article R1123-1 CSP 2nd and 3rd paras). The coordination, harmonization and evaluation of the CPP's activities is committed to a National Commission for Trials Involving Human Subjects, established under the Ministry of Health. According to Article D1123-27, created by decree no. 2016/1537 and integrated in the regulatory part of the CSP. The Commission ensures the coordination and harmonization of the functioning of the CPP, notably by means of recommendations; organizes a meeting of the CPP at least once per year; forwards to the CPP the requests for opinion from the Ministry of Health on all organization's projects likely to impact on their functioning; gives its advice on all issues concerning the interpretation of the texts falling within the exclusive competences of the CPP; makes a summary of the annual reports on the CPP's activities; forwards to all CPP the negatives advices and the analysis for information with a view to developing recommendations; develops the reference document for the assessment of CCP and organises their assessment; and develops a training programme for CPP's members[9].

[9] The whole French regulation on clinical trials with drugs is mainly integrated in the *Code de la santé publique* (CSP), i.e. the French Public Health Code, available at www.legifrance.gouv.fr. Further information on the enforcement of the European Regulation and on the role played by French Ethics Committees as well as by other national authorities (mainly the ANSM "Agence nationale de sécurité du medicament", i.e. the French National Agency of Medicine and Health Product Safety) are available on the ANSM website. Updated information bulletins and practical information guides are also available in English : https://www.ansm.sante.fr/Mediatheque/Publications/Information-in-English [accessed 18 April 2020].

Greece shows quite a similar scenario. Here, clinical trials are subject to authorization by the National Organization of Medicines ("EOF", art. 5 of the Ministerial Decision G5a/59676/2016), on the condition that the National Ethics Committee has issued a favourable opinion. In case of an unfavourable opinion of the National Ethics Committee, EOF cannot issue an authorization for the trial. EOF may also revoke the authorization of a clinical trial, halt a clinical trial or require the sponsor to modify the clinical trial (art. 5 of Ministerial Decision G5a/59676/2016 and art. 77 of the Regulation). The National Ethics Committee of the National Organization of Medicines is the only ethics committee responsible for the ethical review of clinical trials applications[10]. It was established in 2003, by Ministerial Decision DYG3/89292/2003, which provided that the Committee is an independent advisory body, legally residing in the National Organization of Medicines. The operating procedures of the National Ethics Committee were regulated by the Ministerial Decision DYG3A/69150/2004[11]. The Ministerial Decision G5a/59676/2016 orders that both of the aforementioned ministerial decisions will be abrogated as soon as the Regulation 536/2014 comes into force. The new Ministerial Decision G5a/59676/2016 devotes a whole chapter to the National Ethics Committee (Chapter II). Whilst this Ministerial Decision does not provide for a specific accreditation process for the Committee, it does set out rules in respect of its composition, its duties and responsibilities. The Committee is composed and staffed with Decision of the Minister of Health after proposal of the President of EOF. The Committee has to follow Standard Operation Procedures (SOPs), keep written records and minutes of its meetings and to comply with the principles of Good Clinical Practice (GCP) and with the applicable legislation. The Committee has to annually inform the National Organization of Medicines and the Ministry of Health about all of its opinions and to submit to the Health Minister an annual written report related to its activities during the previous year.

In Germany, the accreditation and monitoring system is complex. The formation of ethics committees takes place according to States Law[12]. As a rule, the ethics committees are formed by the medical associations of the states and also at the universities. The university hospitals and these bodies have been able to regulate the composition and

[10] The Ministerial Decision DYG3/89292/2003, which, according to the Ministerial Decision G5a/59676/2016 will be abrogated as soon as the Regulation 536/2014 becomes applicable, provided that the National Ethics Committee, in order to issue its opinion, should take into account the opinion (if any) of the ethics committees established within the regional health system under the provisions of law 2889/2001.

[11] Official Government Gazette n. 1503/ 7.10.2004 (Issue B).

[12] This is conditioned by the federal system.

prerequisites of membership of the ethics committees independently by their own statutes. Until the 23rd December 2016, all clinical trials were supervised by local federal competent authorities (Regierungspräsidien), one in each federal state. Since then, when the first part of the 4. AMG[13] amendment came into force, the authority to set up ethics committees continues to be governed by state law but according to § 41a (1) AMG, the role of the supervisory body in clinical studies may only be assumed by a public-law ethics committee of the states registered with the federal authority. Now the registration procedure and mandatory minimum requirements for the approval of the ethics committee are determined in Sec. 41 a to Sec. 41 c AMG. Sec. 41 a sub-sec. 3 no. 1-7 AMG determines in detail the requirements for the professional composition of ethics committees which comply with the previous recommendations but are now legally binding. All ethics committees must have rules of procedure, an office with qualified personnel and sufficient factual equipment to perform their duties. The ethics committees formed must be registered with the Federal Institute for Drugs and Medical Devices pursuant to Section 41a AMG after the application for registration has been approved by the Federal Institute for Drugs and Medical Devices in agreement with the Paul-Ehrlich-Institut. On each application, the ethics committee must obtain declarations of independence of its members[14]. And, according to Sec. 41b, the Federal Government may issue rules of procedure governing the cooperation of the ethics committees with the federal authorities.

In Italy, no specific accreditation – either by the national Agency/Ministry, nor at the local level – is required. Ethics committees are established within research institutions, according to the existing legal framework. The law (legislative decree 211/2003) regulates in particular: (i) the evaluation criteria; (ii) the amount of the remuneration, when provided; (iii) the criteria for the recruitment of participants; (iv) the terms within which the committee must determine the application (60 days in case of monocentric trial); no prorogation is allowed (except in case of gene therapy and biologicals).

[13] Arzneimittelgesetz: https://www.gesetze-im-internet.de/amg_1976/ [accessed 18 April 2020, in English: Medicinal Products Act: https://www.gesetze-im-internet.de/englisch_amg/indx.html

[14] These declarations of independence shall be made by by the members of the ehtics committee and any experts themselves and not by any authority – see Sec. 3 sub-sec. 7 KPBV, Model declarations can be found in Annexes 1 and 2 to § 3 KPBV (KPBV = Klinische Prüfung-Bewertungsverfahren-Verordnung: https://www.gesetze-im-internet.de/kpbv/BJNR233300017.html [accessed 18 April 2020], English: Clinical Trial Evaluation Procedure Ordinance (no English version available)

In Portugal, clinical trials and clinical studies require a favourable opinion from the competent ethics commission, which can be the Ethics Commission for Clinical Research (CEIC), regulated by Ministerial Order no. 135-A/2014, of 1 July.[15] (for clinical trials and clinical studies involving medical devices) or an Ethics Commission for Health, (entities established by Law-Decree no. 97/95, of 10 May)[16] for all the remaining clinical trials and clinical studies.. Once the corresponding committee provides green light, the trial requires authorization from INFARMED - the Portuguese national regulatory agency – board of Directors.

In Ireland, clinical trial Research Ethics Committees are registered and approved by the Department of Health which is fulfilling the role of the Supervisory Body under the regulations from 2004.[17] There are currently 12 approved committees[18]. The level of monitoring and oversight of these committees from the Department of Health has been traditionally limited. There have been plans for a long time to move the oversight authority for RECs elsewhere, but this has not yet happened.[19]

In Spain, the recently approved Royal Decree has created a specific type of ethics committee that will be the only body empowered to oversee a clinical trial, the Comités de Ética de la Investigación con Medicamentos (Drug Research Ethics Committee). In order to play their role, committees need to gain an accreditation provided by the national or regional corresponding authority. The Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) y las Comunidades Autónomas (Regional Authorities) have established specific common criteria for accreditation, inspection and re-accreditation of these committees. Accreditation is to be reviewed at least every four years by the same authorities that granted the original approval. This system seems particularly interesting in order to guarantee an optimal performance of the ethics committees. There is no limit on the number of these committees. In theory, all ethical committees may ask for the accreditation and it will be obtained if they manage to satisfy the adopted criteria.

In Sweden, the Ethics Review Authority is a state authority under the Ministry of Education. It reviews the conduct of research according to the Sweden Swedish Code on

[15] http://www.ceic.pt/documents/20727/38721/Portaria+n.%C2%BA+135-A-2014%2C+de+1+de+julho/f83a1769-91be-4fb8-84cf-4ddc21d0717e [accessed 18 Sept 2018]
[16] https://dre.pt/web/guest/pesquisa/-/search/513633/details/normal?perPage=50&q=Lei+n.%C2%BA%2010%2F97 [accessed 18 Sept 2018]
[17] https://health.gov.ie/implementation-of-eu-directive-on-good-clinical-practice-in-clinical-trials/ [accessed 2 May 2019]
[18] http://www.eurecnet.org/information/ireland.html [accessed 2 May 2019]
[19] https://www.ria.ie/sites/default/files/clinical_trials_expert_statement_final_version_0.pdf [accessed 2 May 2019]

Ethical Review Concerning Research Involving Human Beings (SFS 2003:460). The authority started its operations on January 1, 2019 and then replaced regional ethics review boards. The authority is divided into six regions located in the different parts of the country. Each region consists of several sections, and there is a total of 18 sections in the country who supervise all research conducted on human beings in Sweden. Each of the regional sections of the Ethical Review Authority consist of one chairman and fifteen other members. Ten of the members shall have scientific competence and five of the members must represent general interests. The government appoints the chairmen and alternates for these. Those appointed shall be or have been regular judges. The Ethical Review Authority shall appoint members and alternates with scientific competence as well as members and alternates who represent public interests. There is also a supervisory Ethics Review Appeals Board. A rejection by a regional ethics review board can be appealed to this Board.

Belgium deserves a particular comment. Through recommendations and feedback, this independent body (the college) indirectly controls the quality of the local ethics committees. At first glance, this seems a rather weak mechanism of oversight. However, the Belgian regulation has developed a procedure to suspend the accreditation of the ethics committee on the request of the College and the Federal Agency for Medicines and Health Products. Furthermore, as the College is in charge of the allocation of the committees, it could sideline an ethics committee, by systematically not allocating them to a clinical trial evaluation case. As such, each ethics committee will be implicitely forced to properly take into consideration the feedback of the College. Since the ethics committees are subsidised based on the number of cases dealt with, they will also have a financial incentive to take into account the feedback of the College (art 34/1 wet 7 mei 2004). Finally, it is worth mentioning that the Portuguese and the Greek systems are based on a single committee system, and no formal mechanisms to monitor its performance have been developed. However, its members can be held liable for their actions. Therefore, misconduct seems unlikely in these countries.

In light of the above, we can conclude that in most of the Member States examined, accreditation and monitoring systems are quite similar and adequately designed to fulfil their function. As a result, it seems reasonable to assume that freedom of competence will be unlikely to induce unethical or corrupt practices in the ethics committtees involved. In that sense, it is perfectly possible to conclude that a harmonized monitoring system has

been implemented in practice through the adoption of common standards of supervision in almost all analyzed Member States (Italy might be an exception to this general rule, since the accreditation system does not exist as such – ethics committees do not need an official accreditation – a circumstance that creates significant variations in the quality of the committees).

Finally, it is neceesary to mention that, where committees need to gain an accreditation to operate, it is difficult to see how any of the accreditation systems are inadequate. Thus, competition between them is unlikely to result in any form of ethical dumping as the existing supervisory system should make this impossible. Therefore, any strategy that seeks to maximize the attractiveness of a committee to a clinical trial sponsor must be based on outstanding performance of the committee as such.

3.- The System for Assignment of Cases to Ethics Committees

The assignment system plays a key role in the performance of ethics committees. If trials are assigned randomly or on the basis of geographical or other fixed criteria, it is less probable that they will do their best to receive more applications, since their efforts will not be rewarded with a higher number of trial supervisions. On the other hand, if the sponsor can decide which supervisory body will play this role, ethics committees may seek to perform their tasks efficiently so as to attract more applications, particularly if they receive extra funding as a consequence This is precisely the scenario in Spain, where sponsors are totally free to choose the Ethics Committee that supervises the clinical trial and committees receive additional funding according to the number of trials monitored (see next section).

Similarly, in Ireland the sponsor or researcher chooses the research ethics committee for the review of the clinical trial. No guidance or restriction is placed on the choice of the committee. However, individual committees might refuse to consider applications on the basis of review capacity (some committees only review a specific number of applications per session and will refer additional applications to a later review session). The approval by that research ethics committee applies to any research site in Ireland (unlike the local/institutional system in place for non-clinical trials). However, a trial site can refuse to host an approved trial based on resources or on ethos (i.e. religious

objections to the trial, e.g. Catholic hospitals refusing to host trials that involve the use of contraceptives).

In Belgium the system is not as flexible as in Ireland or Spain, but still leaves some room for choices to be made on the basis of performance of the various ethics committees. The College appoints which ethics committee to evaluate the clinical trial, based on a rotation system between the different ethics committees. Moreover, the Belgian law of 7 May 2017 explicitly states that the ethics committee cannot evaluate a clinical trial that will be performed at the same hospital as to which the ethics committee belongs to (Wet klinische proeven, 2017). However, despite these restrictions, the College can take into consideration the respective areas of expertise and quality systems of the ethics committees in this decision (art. 22 KB). Moreover, the Belgian legislator gave the College the freedom to elaborate a more detailed standardized procedure for this allocation in its internal regulation (art. 29 KB).

In some other countries, this kind of freedom does not exist. For instance, in Greece, there is only one national ethics committee responsible for the ethical review of clinical trials applications. In Denmark, there are a number of committees, but the sponsors cannot choose between them. Generally, the committee to which a case is assigned will depend on its competency. In cases of multi-centre trials then the investigator should only apply to one committee, the one that is in the located in the area where the principal investigator is carrying out the research project.[20] Therefore, two factors determine the allocation, competency and location, and the sponsor can do nothing to influence the selection.

In France, there are 39 CPP divided up into 7 regions, with an average of 5 to 6 CPP per region (except for the Ile de France region around Paris which has 10 CPP). They are all competent for the specific region, while having at the same time a national competence. After the entry into force of the new French regulation of clinical trials involving human subjects, the CPP is randomly appointed (Article L1123-6 CSP)[21]. Within the CPP, the President designates two rapporteurs and each opinion must be supported by reasons. In case of negative advice by the appointed CPP, the sponsor can

[20] Information found on the National Science Ethics Committees website: http://www.nvk.dk/english/the-system-of-health-research-ethics-committees [accessed 12 Sept 2018]

[21] Law no. 2018-892 concerning the "désignation aléatoire des comités de protection des personnes" has specified that the CPP is randomly appointed among those committees which are available and have the necessary expertise to assess the project ("parmi les comités disponibles et disposant de la compétence nécessaire à l'examen du projet"). Moreover, starting from July 2018 exchanges between the sponsors and the CPPs are managed by the so called "système d'information des recherches impliquant la personne humaine".

ask the Ministry of Health to submit the refused application to another committee for a second review (Article L1123-6, 2nd par., CSP)[22].

In Germany, the situation is quite different, since there are several ethics committees, but the final result in terms of competence is the same, since trials supervision is assigned to the committees on the basis of fixed variables. For many years, the geographical factor was the key determinant. Indeed, the ethics committee was responsible for evaluating a clinical study in whose region or area of responsibility the head of the study was based. At present, the factors for selection have changed, even if the lack of freedom for sponsors remains the same. According to § 41 b (2) AMG in conjunction with § 4 KPBV[23], the registered ethics committees prepare an annual responsibility distribution plan in advance. Appraisal requests will be assigned to the respective ethics committee in the order of this responsibility distribution plan. Therefore, what has been implemented is a shift system. For example, the ethics committee which is in the 6th place on the distribution plan will consider the 6th request made and so on.

In Italy, the framework also offers limited scope of selection for sponsors. According to the legislative decree 211/2003, the competent ethics committee will be the one established within the institution to which the researcher belongs. In the case of multicentre trials, a justified opinion will be provided by the committee of the institution to which the coordinator belongs (art. 7). In case of industry-sponsored trials, however, the industrial sponsor is allowed to designate the coordinating centre (and, accordingly, the competent ethics committee to which the coordinating centre refers to). Other interested committees can communicate opinions to the competent ethics committee but they can only accept or reject the positive decision of the competent committee. Other interested committees can only modify the content of the informed consent and consequently subordinate the participation to the trial to the acceptance of these modifications.

In Portugal, the situation is more complex. As already demonstrated, there is only one CEIC, which supervises all clinical trials and studies that involve medical devices. However, the CEIC can appoint an Ethics Commission for Health (known as “CES”) to

[22] On the role of CPP see also IGAS Report no. 2013-103R *“Evolution des comités de protection des personnes (CPP) évaluant les projets de recherches impliquant la personne humaine, après la loi "Jardé" du 5 mars 2012*”„ available at http://www.igas.gouv.fr/IMG/pdf/Rapport_2013-103R_CPP.pdf [accessed 18 Sept 2018]

[23] Klinische Prüfung-Bewertungsverfahren-Verordnung: https://www.gesetze-im-internet.de/kpbv/BJNR233300017.html [accessed 18 April 2020], English: Clinical Trial Evaluation Procedure Ordinance (no English version available)

undertake the supervision. On the other hand, clinical trials and studies that do not involve medical devices are supervised by the various CES. There are several CES operating in private and public health units. The competence of each CES is established by the location in which the clinical trial or studies is performed. If the trial or study is to be performed in a location that does not have its own CES, the CEIC designates a CES (from another unit) to control the trial or the study

Finally, in Sweden trials supervision is assigned by the central authority to a regional section of the authority. The application procedure is centralized and the researcher may not select which regional ethics review board that will assess the application. This system aims to create an impartial and effective system for rapid and high quality assessments. The supervisory Ethics Review Appeals Board gives possibility to appeal a rejection by a regional ethics review board.

According to this comparative analysis of the legal framework, it seems that the Spanish or Irish system might be more effective to improve the quality of the performance of the ethics committees. Indeed, since sponsors are free to choose the committee that will supervise the trial and the committees are willing to supervise as many trials as possible, it is quite easy to suggest that the regulations have created a highly competitive system. Assuming that neither of these committees tries to cheat the system by reducing the level of ethical requirements (which seems unlikely, according to the analysis made above), their best way to attract resources will be to do their job efficiently and effectively. It is therefore reasonable to conclude that in Spain at least, the number of committees supervising the majority of clinical trials will be reduced in the future. Moreover, some of these committees are likely to be particularly attractive due to their high degree of expertise.

In the Belgian system, the committee is selected by the College, which has accordingly a decisive influence on the behaviour of the committees (insofar as the assignment of trials to specific committees is an effective way to let committees understand the ways in which the College wants them to perform their work). This might imply that in the future the College will be able to reward competence by assigning a higher number of trials to the best performing committees, a policy that would surely improve the functioning of the general system. The main contrast with the Spanish system is that in the Belgian framework it will not be the sponsors but an institution, The College, which will make the difference between committees.

Conversely, in countries such as Germany, the allocation of shift supervision is likely to reduce the incentives for committees to exercise their tasks more flexibly and efficiently. The mere compliance with legal standards will be sufficient to consider that they have satisfactorily fulfilled their mission, so it will be difficult to produce innovative initiatives that improve their efficiency, although the distribution key is intended to guarantee an even distribution of procedures and thus planning and legal certainty for the individual ethics committees and may ensure neutrality and independence. Countries such as Greece do not really promote an efficient competence system, since there is only one ethics committee responsible for the ethical review of clinical trials.

The case of Italy is more nuanced. On the one hand, the determination of the competent committee is linked to institutional relationships. On the other hand, in addition to the industrial sponsors' prerogative to designate the coordinating center in multicentre trials (and thus choose accordingly the relevant ethics committee in charge of the trial), an induced form of competition among committees is fostered by delegated law n. 3/2018. Such legislation stipulates that the total number of committees in Italy will be reduced to 40 (there were around 300 Committees in 2003, while their current number is down to 90). Insofar as the number of opinions issued by each committees is among the main criteria that the Italian Medicines Agency (AIFA) will adopt in order to choose which of the current 90 committees will be able to continue their activities, this is likely to pressure committees towards capturing as many trials as possible.

Finally, the French system deserves particular comment. On the one hand, its randomized system for the assignment of cases is clearly inefficient to stimulate a general improvement of the quality of the performance of the committees through the logic of competence and capacity. However, the fact that the sponsors are given a chance to receive a second opinion serves in practice as a system to stimulate performance. Committees will probably be reluctant to receive implicit criticism by second opinions delivered by colleagues. Therefore, this may serve as a system to motivate performance.

To sum up, we conclude that the ethics committee assignment systems vary substantially in the Member States that we have analyzed, challenging the vision of harmonisation. This can be problematic to the extent that the diverse allocation systems permit significant differences to arise, in terms of motivation and performance between committees. Committees that are aware that an excellent performance will be rewarded with an increased number of supervisions are more likely to seek to improve their performance compared to those where performance will bring nothing, apart from some

kind of intrinsic satisfaction. Of course, one might think that some committees are not so willing to increase the number of supervisions made and, thus, it is not so clear that all those who are offered this chance will make the additional efforts to reach excellence. This objection would be sustained if it were not true that in some systems (mostly flexible systems) the volume of monitoring performance is associated with the level of funding received by the committees, as we will show in the next section.

4.- Economic issues

Economic issues play a key role in the performance of ethics committees. As a report by the Nuffield Council stated, "…committees may be ineffective for a variety of reasons, including a lack of financial and human resources, and a lack of training in, and experience with, reviewing the ethics of research."[24] Indeed, research ethics committees require administrative and financial support. In its absence, the quality of their performance might decrease. To begin with, the adequacy of budget allocation will play a key role in terms of recruiting and training committee members, a variable that is highly relevant to their performance.[25] On the other hand, if no fees or compensation are provided, members of research ethics committees may not be able to provide the necessary time and expertise to review research in a timely manner.

These circumstances are particularly worrying in the framework of the new Regulation on Clinical Trials, since delivery terms are undoubtedly exigent. Therefore, any prediction about the performance of ethics committees in the EU member states must be based on adequate information about the resources available to the committees and their members. This final part of our work will be focused on this topic. For this purpose, we have divided the analysis in four main parts, corresponding to four main factors that conditionate the committees' performance: the sources that fund the existence of the committees as such; if sponsors are obliged to pay fees for the review and whether these fees (or part of them) are finally allocated to the committees; if the committees' members

[24] Nuffield Council on Bioethics, 'The Ethics of Research Related to Health Care in Developing Countries' April 24th 2002, chapter 8, p. 103. Available at: http://nuffieldbioethics.org/wp-content/uploads/2014/07/HRRDC-I-Chapter-8-Ethical-review-of-research.pdf [accessed 8 Sept 2018]
[25] G. Ricci, N. Cannovo, 'The importance of the training of Ethics Committee members' (2009), *Med Law.* 28(4), 649–59.

receive any kind of compensation or fee for their work; and the possibility to outsource part of their work to independent professionals.

4.1.- Sources of funding

The first variable to be analyzed is whether the committees receive any kind of permanent funding and where it comes from. This is a fundamental factor, since it might explain differences in their performance. For instance, if they are funded by a regional government, some committees might have a much bigger budget than others in the same country and thus their capability to train the committee members or to hire a permanent technical secretariat would be dramatically different.

According to the data gathered by the authors of this paper, the situation varies between the countries analyzed. In some of them, committees are funded by a national authority and no differences in budgeting can be traced. In the rest of the countries analysed, funding of the committees is somehow linked to the fees paid by the sponsors, as the next section will show.

Our initial focus will be on those countries where ethics committees are funded by public authorities of some kind, or those that incorporate a mixed system. In France, CPPs are state-funded (Article L1123-1 CSP) and subject to the budget, financial and accounting regime provided for by decree no. 2012-1246 on the public budget and accounting management, which applies to CPPs with the exceptions mentioned in article R1123-19 CSP. In Greece, the National Organization of Medicines is responsible for providing the National Ethics Committee with appropriate space and modern and appropriate IT equipment and secretarial support. The relevant expenses of the National Ethics Committee, as well as the expenses for the committee members' travel and accommodation (in case they live outside Athens) burden the budget of the National Organization of Medicines (article 22 of Ministerial Decision G5a/59676/2016).

Conversely, in countries such as Denmark or Portugal, there are differences according to the type of committee involved. In Denmark, regional committees are financed by the regions and the national committee is financed by the Ministry of Health and Elderly (§1 Executive Order no. 1159 and §40 Executive Order no. 1083). In Portugal, the members of the Ethics Commission for Clinical Research (CEIC) are part of the National Institute of Pharmacy and Medicines (Infarmed) staff, thus, it could be said that Infarmed is funding a part of the supervision of clinical trials. However, CES's are funded by the health unit in which they are located.

In Spain, the system is totally different: each CEIm (Comités de Ética de la Investigación con medicamentos/ Ethics Committees for investigation with medicinal products) is funded by the institution it is rooted in, but they can receive extra funding from the AEMPS according to their active involvement in clinical trials review process. Similarly, in Ireland committees are funded by the institution that hosts them and use the fees obtained from clinical trials to subsidise their institutional function of reviewing research taking place within their institution or conducted by their staff. Finally, in Germany, there is a mixed system of funding. The basic funding is provided by the respective institution of the ethics committee, i.e., the university clinic or the medical association. The activities of the ethics committees are then additionally supported by fees. A similar system exists in Sweden. The regional committees are supposed to be fully funded by the applications fees from the university clinic or the medical association. However, this is complemented by public funding by the Government due to higher costs that the sum of the application fees[26]. There are, at times, discussion whether to increase the applications fees to fully compensate for the costs of the Ethics Review Authority's work.

4.2.- Potential to charge fees

The situation regarding fees is very different in the countries subject to analysis. First of all, there are some countries where no fees are charged at all. In Greece, the National Ethics Committee simply does not charge fees to the sponsors and, in general, does not charge the parties involved in the conduct of the clinical trial (fees are however charged by the National Organization of Medicines, responsible for the authorization of the clinical trial). Similarly, in France and Belgium no fees are charged to the sponsors. No proof of payment of duty needs therefore to be provided to access the assessment procedure.

The majority of countries studied choose a different policy and permit the charging of fees. In Denmark, Ethics Committees charge fees. The fees charged differ between the processing of health science research trials and the processing of changes to an already approved trial. According to §3 of the Act above, in the former the fee will be 4,850 DKK and in the latter 1,819 DKK. Nevertheless, §4 states that the amount is adjusted every

[26] U2017/05023/BS; https://www.esv.se/statsliggaren/regleringsbrev/?RBID=18553) [accessed 8 Sept 2018]

year and the most up to date information on the website indicates the prices to be 5,223 DKK and 1,959 DKK respectively (§1-8 Executive Order no. 1159). Similarly, in Portugal article 48 of Law no. 21/2014 states that "for the services provided within the scope of this law are due fees to be set by ordinance of the members of the Government responsible for the areas of finance and health." The fees are currently established by Ministerial Act no. 63/2015, from 5 March.[27] However there might be some exceptions to this general rule. The mentioned Act provides that Informed Board of Directors can exempt some clinical studies from costs considering the nature and purpose of the study, whenever the sponsor of the study is a non-profit institution or if the study has non-commercial nature.

In Sweden and Germany fees are compulsory. In Sweden the existence of the committees is dependent on the charges for applying for ethics review. A fee is charged for each application of ethics review. The fee is approximately 500 euro for an application that concerns one main research group, and up to 1600 Euros for other groupings. For drug trials the charge is always 1600 Euros. The application should be submitted by the responsible research body, i.e. the state authority or the physical or legal entity under whose auspices the research is to be conducted. This body has the ultimate responsibility for the research and should therefore formally apply for ethical vetting. In Germany, all ethics committees charge fees to the sponsors. In general, this is regulated in the statute of the ethics committee with reference to the fee directive of each state. According to the new § 41b para 2 AMG n. F.[28] ethics committees are now obliged to indicate the fees for their activity in their rules of procedure.

In Ireland, ethics committees charge fees for commercially funded trials; fees are often waived for trials that are not funded by the pharmaceuticals industry. There is no national fees structure; individual committees set the level of fees. Studies from 2012[29] and 2010[30] highlighted the general under-resourcing of most Irish Research Ethics

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[27] https://dre.pt/web/guest/pesquisa/-/search/66888637/details/maximized?print_preview=print-preview. [Accessed: 06 Sept 2018].

[28] n. F. means 'new version'

[29] HIQA (2012) 'International Review of Research Ethics Structures' p.18. Available at: https://www.hiqa.ie/system/files/Intl-Review-Research-Ethics-Structures.pdf [Accessed: 06 Sept 2018]

[29]Felzmann, Heike, Sixsmith, Jane, O'Higgins, Siobhan, NicGabhainn, Saoirse & Ui Chonnachtaigh, Sorcha (2010)) 'Ethical review and childrens research in Ireland'. Office of the Minister for Children and Youth Affairs (OMCYA). p.34. Available at: https://aran.library.nuigalway.ie/bitstream/handle/10379/6159/Ethical_Review_and_Childrens_Research_in_Ireland_Report.pdf?sequence=1&isAllowed=y [Accessed: 12 Sept 2018]

[30] https://dre.pt/web/guest/pesquisa/-/search/66888637/details/maximized?print_preview=print-preview [Accessed: 06 Sept 2018]

Committees. At the time, resource allocation was fully dependent on a combination of (i) the resources of the hosting institution as well as (ii) the fees obtained from review of trials.

The Spanish system is quite different, since the committees as such do not charge fees to the sponsors. They will pay a fee to the AEMPS and this public body will pay back a part of it to the corresponding CEIm. In Greece, as already mentioned, fees are paid to the National Organization of Medicines that authorizes the clinical trial (at standard amount depending on whether authorization is sought for the conduct of a new trial or the amendment of an existing trial). In Portugal, according to article 48 of Law no. 21/2014, fees for the services provided within the scope of this law are to be set by ordinance of the ministries of finance and health. The fees are currently established by Ministerial Act no. 63/2015, from 5 March.[31] This act provides that the Board of Directors can exempt some clinical studies from fees considering the nature and purpose of the study, whenever the sponsor of the study is a non-profit institution or if the study has non-commercial nature.

Finally, in Italy the delegated law n. 3/2018 (geared to the implementation of Regulation 536/2014) calls for the establishment of a common national fee. At the moment, however, there is not a general common rule at a national level; each Committee can define a fee, which can be waived when the research is non-profit (independent research).

5.3.- Remuneration of Committee Members

Our analysis finally focuses on the rewards, fees and compensation offered to the members of the ethics committees. This is a vitally importantissue, since professionals do not usually wish to spend much of their working time on a low-paid activity. Moreover, chairs and administrators who receive the same resources, regardless of the workload they face are expected to be less motivated to optimise their performance than those who receive support depending on the tasks performed. Again, differences between countries and even between different types of committees in the same country are significant.

In Denmark, the members of the ethics committees receive some compensation for their participation in the committees. The chairman and vice-chairman of the National Science Ethics Committee and the 7 members appointed pursuant to §38(1) no. 2 and 3

[31] https://dre.pt/web/guest/pesquisa/-/search/66888637/details/maximized?print_preview=print-preview [accessed 8 Sept 2018]

are paid in agreement with the Ministry of Health whom bears the cost (§40(3) Executive Order no. 1083). Members appointed pursuant to §38(1) no. 4 receive compensation for documented loss of earnings and expenses allowance (§40(4) Executive Order no. 1083).

In France, CPP members participate in the committee's activity without payment. Members suffering a loss of income due to their participation in CPP sessions, as well as experts, specialists and reporters benefit from a financial compensation. The amount and the conditions of this compensation are fixed by decree (*arrêté*) of the Ministries of budget and health (Article R1123-18 CSP, 1st and 2nd paras). They also receive an allowance for their travel and overnight stay expenses under the conditions provided for by the regulation applicable to State civil servant (Article R1123-18 CSP 3rd par.).

In Greece, the members of the National Committee do not receive a salary nor are they exclusively dedicated to the Committee. Given that the Committee is based in Athens, where its meetings are held, the travel and accommodation disbursements of the members who don't have their residence in Athens burden the budget of the National Organization of Medicines (Article 22 of Ministerial Decision G5a/59676/2016).

In Ireland, members of clinical trials committees have traditionally not received financial compensation or salaries, with the exception of occasional travel expenses for some members, and in extremely rare cases fees for particularly sought-after expertise. In Italy, instead, the members of the ethics committees usually receive a nominal attendance allowance, in addition to compensation for travel expenses and similar costs in which they could incur.

In Portugal, there is a mixed system. The members of the Ethics Commission for Clinical Research (CEIC) are part of the Infarmed working staff and thus paid by this institution, even though CEIC and Infarmed are autonomous. In order to maintain their independency, article 8 of the Ministerial Order no. 135-A/2014 states that its members cannot have any kind of interest (economic or of other nature) in the pharmaceutical industry susceptible of affecting the impartiality of their decisions. Thus, it can be stated that the members of the CEIC are professional, since they are paid to do this job. In contrast, members of the CES, do not receive any payment, except for the reimbursement of transportation expenses (article 12 of Law-Decree no. 97/95)

The same happens in Spain. While the members of the Committees do not receive any fees (but only *per diem*), the secretary of the board can be a professional paid by the

institution where the Committee is allocated[32]. Quite similarly, the German system contemplates that all ethics committees have full-time members. These are at least the management and the employees of the office (Sec. 41 a sub-sec 3 no. 5 AMG). Also several Ethics Committees provide their members with allowances, reimbursement of travel expenses. But some do not. It depends on the statute of the ethics committee.

In Sweden, the system is different, since the members of the ethics committee receive an allowance for each meeting that depends on the number of applications that are reviewed and the specific workload for each member of the committee. Therefore, one could expect an interest in addressing a higher number of applications; however unlikely as the allowance is very low and the fees are not determined by the committees. The applications are primarily distributed to the members of the board based on their individual expertise and impartiality, and the goal is to distribute the work as evenly as possible within the group.

5.4.- Potential to Enter into Consultancy Arrangements

Finally, consultancy is also a variable that must be kept in mind, this is due to a simple reason: if ethics committees are allowed to invite/seek assistance from an external expert if needed, this should improve their performance. Therefore, countries that allow this practice provide their ethics committees with an adequate tool to deliver excellent performance. According to the data gathered, the situation varies significantly between different countries. For instance, regulation of this issue is extensive in France. The CPP may include one or more experts, whose expertise is required for the nature of the research project. As a rule, they can attend the committee sessions without voting power and their advice must be given in a written report (Article R 1123-13 CSP). Considering the technical nature of the research project, the President of the CCP may appoint external experts on his own initiative or upon the request of the dossier rapporteur.[33] In specific cases, expressly provided for by the law, external experts not only attend committee sessions, but also participate in the decisions concerning a given research involving their expertise. Research projects involving minors or adults unable to give their consent

[32] However, it is important to note that the members of the committees are staff of the hospitals performing other tasks and the secretary of the committee, although professionally devoted to the committee, has no vote in its decisions.

[33] Decree (Arrêté) of 13 January 2010 regarding the internal regulation model to be adopted by the CPP

(Article R1123-14 CSP), as well as research carried out in the field of assisted reproduction are cases in point (Article R1125-19 CSP).

In Denmark, the committee is permitted to make use of consultancy services where it doesn't possess the necessary professional expertise to assess the projects (§22 Executive Order no. 1083). The same position pertains in Spain. However, the regulation is unclear on the issue of whether external advisors can receive fees for their assessments. In Germany, ethics committees can transfer aspects of their work to external consultants (Sec. 42 sub-sec. 1 AMG). In Greece, the National Ethics Committee is allowed to consult any person deemed appropriate in cases/research proposals that need specialized assessment, under the condition that this person is not involved in the clinical trial concerned, does not have any direct or indirect interests related to the parties involved and that they are committed to maintaining confidentiality. Consultants participate in the relevant meeting of the Committee as an expert with no right to vote. Similarly, in Italy, Ministerial Decree 8 February 2013 provides that "in case of issues not covered by the expertise of members, the committee may call for ad hoc opinions, external experts" (Art. 2.6). In Ireland, a research ethics committee may seek the advice of an external expert on any aspect of an application for a clinical trial involving a medicinal product, where the knowledge is beyond the expertise of the existing members, provided any interests are declared.[34] On the other hand, in countries such as Belgium or Sweden, the use of consultants is not specifically permitted by the national regulatory framework.

5.- On the way to harmonization?

As outlined above, the characteristics and contexts of ethics committees vary considerably between, and sometimes even within, Member States. We concede, of course, that most of them have implemented efficient accreditation and control systems that ensures an adequate performance by all ethics committees. However, the scenario regarding the assignment of the supervision of clinical trials demonstrates significant differences between the studied countries. Indeed, our data shows that this issue depends on a wide range of criteria. In some countries, fixed factors, such as geography, for instance, determine the committee to which the application will be allocated. In some others, this will depend on the will of an institutional body (Belgium) or be left to the decision of the sponsor (Spain or Ireland). Therefore, rather than a unique, harmonized

[34] https://health.gov.ie/wp-content/uploads/2014/06/rec_guidance_2012.pdf (p.13) [Accessed 2 May 2019]

framework, we should talk about a highly fragmented scenario, with significant differences between Member States.

The same could be said about financial aspects. There is a common policy in that members of ethics committees do not receive fees for their participation. However, this uniformity does not extend to the funding of the committees. On this point, substantial divergences arise again. As we have described, there are some countries where ethics committees receive a fixed budget, no matter what they do. In some others, their funding might vary according to a number of factors that, in general, are not linked to the committee's performance. Finally, there are countries that allow an unequal distribution of funds, directly linked to the volume of supervision work developed by each committee, such as Ireland, Spain and, to a degree, Belgium.

The system implemented in these countries creates a scenario of progressive concentration of supervision in a small number of committees. This is precisely what happened in Ireland, a country where sponsors could choose the Research Ethics Committee (REC) for the review of the clinical trial with no restriction or guidance. The final result of this process is easy to describe: a very small number of clinical trial RECs in Ireland traditionally reviewed a large share of all applications, allowing the most attractive RECs to develop a better funded infrastructure; for most other committees there did not appear to be a particular interest in capturing as many trials as possible. This scenario is repeated in Spain. According to the data at our disposal, there are 88 ethics committees, but only 8 of them (<10%) accumulate more than a 50% of the clinical trials supervision. Moreover, an 80% of the monitoring is performed by only 20 committees (<25% of the total).[35] Finally, it may happen to be the same in Belgium, since the amount of the subsidies that Belgian hospitals receive to compose and maintain ethics committees depends on the number of processed cases by each committee. However, the Belgian scenario is more difficult to foresee, since sponsors will not be able to choose the ethics committees. Rather, they will probably be rewarded according to their productivity. Thus, it seems that some of them might stand out over the rest.

In conclusion, we have evidence to suggest that in countries where committees are somehow rewarded by their performance, supervision tends to concentrate in a quite small

[35] Source: BDMetrics, 2018, p. 31. At: https://www.medicamentos-innovadores.org/sites/default/files/medinnovadores/Espa%C3%B1ol/Informe%20BEST/Informes%20semestrales/2017/Resultados%20BDMetrics%2024%C2%AA%20publicaci%C3%B3n.pdf. Last accessed: 27/04/2019.

group of these supervisory bodies, This is probably due to the fact that these ethics committees are highly motivated to optimize their performance so as to maximize the number of applications gathered and the rewards obtained. Moreover, better funding allows them to hold well-structured and trained technical offices and to support their members performance with adequate budgeting. As a final result, we could expect that these countries highlight some significant differences between committees. This would unlikely be the case in the Member State countries where committees are not rewarded according to their performance. Moreover, we could even expect that countries promoting such excellent performances allocate a proportionally higher number of trials than the others, at least if all other factors that induce sponsors to choose a country to perform a trial remain the same – such as patient recruitment, financial costs, accessibility to research system at national and pan-European levels and so on.[36]

We conclude that, on the one hand, the monitoring and control system designed to guarantee an adequate performance by the ethics committees at the national level shows very similar characteristics in all the EU Member States analyzed. Therefore, the level of harmonization in practice is high and no further actions seem needed. On the other hand, there are reasons to believe that most of the rules regarding the composition and functioning of the committees are also very similar across the EU. They are mostly composed by volunteers who do not receive fees for their participation, but only adequate compensation for their attendance to the meetings and so on. Thus, no further harmonization is needed in this part, too. However, the situation changes when we think about the system of funding and resources available to the committees. As we have shown, there might be huge differences between countries in this regard. Moreover, these differences might create two different structures: countries where a quite small number of committees are specially appreciated for their excellent performances (reached thanks to a higher budget available), and countries where this situation is less evident.

At these first stages of the implementation of the Regulation, it is hard to know if these differences will bring substantial consequences to the allocation of clinical trials in the EU. It is also difficult to know if the concentration of the supervision in a few highly skilled committees might be preferable to an alternative scenario with less concentration of monitoring. In any case, harmonization is not particularly compatible with such

[36] M. Gehring, R.S. Taylor, M. Mellody, et al 'Factors influencing clinical trial site selection in Europe: the Survey of Attitudes towards Trial sites in Europe (the SAT-EU Study)', (2013), *BMJ Open*. doi: 10.1136/bmjopen-2013-002957.

different alternatives and at some point it might be necessary for the EU to provide Member States with guidance on how to address these issues.

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