

Clinical Trials Law and Policy:  
Human Subjects Protection and Global Dynamics

Dissertation

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## INTRODUCTION

This thesis deals with the implications of clinical research – specifically, clinical trials – in terms of law and policy at the international level. This introduction briefly presents the thesis and introduces some of the research developments explored following the thesis defense that took place in Jena on December 10, 2018.<sup>1</sup>

First, some preliminary notions are worth introducing. For the purpose of this thesis, the concept of clinical trials is intended to comprise “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.”<sup>2</sup> The element of human participation distinguishes clinical trials from other stages of clinical research and chronologically places them after laboratory-based research development activities and animal testing.<sup>3</sup>

While clinical trials encompass a variety of activities, the first way in which such activities can be categorized depends on chronological phases. Clinical trials are generally conducted on the basis of a four-stage model in which Phase I tests a treatment on a small group of human subjects (e.g. 20-80 participants) in order to test the safety of the treatment and identify major side effects; Phase II widens the human subjects pool (e.g. 100-300 participants) in order to test the effectiveness of the treatment; Phase III further widens the human subjects pool and finalizes the assessment of the treatment; finally, Phase IV, takes place following the entry of the product on the market and further tracks its safety and efficacy.<sup>4</sup> A second traditional way of distinguishing clinical trials regards their design (e.g. interventional, observational, or expanded access).<sup>5</sup> Finally, a

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<sup>1</sup> Mandatory attachments to this thesis were not modified following the thesis defense and, therefore, remain unchanged in this copy. The only edits implemented regard this section and the inclusion of a slide deck utilized during the thesis defense in the “Additional Documents” section.

<sup>2</sup> “Clinical trials.” *WHO*, World Health Organization, [www.who.int/topics/clinical\\_trials/en/](http://www.who.int/topics/clinical_trials/en/).

<sup>3</sup> “What Are Clinical Trials?” *National Heart Lung and Blood Institute*, U.S. Department of Health and Human Services, [www.nhlbi.nih.gov/studies/clinicaltrials](http://www.nhlbi.nih.gov/studies/clinicaltrials).

<sup>4</sup> “Glossary of Common Terms.” *National Institutes of Health*, U.S. Department of Health and Human Services, 10 Feb. 2016, [www.nih.gov/health-information/nih-clinical-research-trials-you/glossary-common-terms](http://www.nih.gov/health-information/nih-clinical-research-trials-you/glossary-common-terms).

<sup>5</sup> “Glossary of Common Site Terms.” *ClinicalTrials.gov*, [clinicaltrials.gov/ct2/about-studies/glossary#study-type](http://clinicaltrials.gov/ct2/about-studies/glossary#study-type).

third way in which clinical trials can be categorized depends on the geographic area in which they take place (e.g. exclusively in one country or simultaneously in more than one area of the world).

In this context, the rationale behind this thesis's focus is three-folded and builds on three elements:

(i) As the clinical trials business grows, clinical trials standards and legislation are becoming an increasingly popular and complex topic.<sup>6</sup> In 2016, the global clinical trials market size was valued at USD 40 billion, and the same market is expected to reach USD 65.2 billion by 2025.<sup>7</sup> In this thesis we argue that the *flourishing of the clinical trials sector* results in an increased need for both institutional and private actors in the legal and medical field understand the challenges and opportunities that the growth of clinical trials poses.

(ii) The field of clinical trials is not only a complex one – both from the scientific and the regulatory standpoint – but also an area of law and policy in which *global interconnections and dynamics are increasingly prevalent*. The increasingly international dimension of clinical trials can be observed in the light of two sets of challenges. The first deals with the conduction of multi-regional clinical trials, in which a multitude of human subjects are simultaneously recruited in a variety of countries.<sup>8</sup> The second is connected with the outsourcing of clinical trials “overseas,” where sponsors (more often than not based in developed economies) decide to finance and conduct clinical trials in jurisdictions different than their own (in some instances, developing economies).<sup>9</sup> In this thesis, we take the stand that both sets of challenges and their incidence on the action of clinical trials' stakeholders support the development of clinical trials-related research with an international outlook.

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<sup>6</sup> Tereskerz, Patricia M. *Clinical research and the law* (Hoboken, New Jersey, Wiley-Blackwell, 2012).

<sup>7</sup> Respectively, “Get free access to The Grand Library, a BI enabled research database.” *Clinical Trials Market Size, Share, Growth, Analysis Report, 2014-2025*, [www.grandviewresearch.com/industry-analysis/global-clinical-trials-market](http://www.grandviewresearch.com/industry-analysis/global-clinical-trials-market) and “Get free access to The Grand Library, a BI enabled research database.” *Clinical Trials Market Size Worth \$65.2 Billion By 2025*, [www.grandviewresearch.com/press-release/clinical-trials-market](http://www.grandviewresearch.com/press-release/clinical-trials-market).

<sup>8</sup> Cf. Shenoy, Premnath. “Multi-Regional Clinical Trials and Global Drug Development.” *Perspectives in Clinical Research*, Medknow Publications & Media Pvt. Ltd., 2016, [www.ncbi.nlm.nih.gov/pmc/articles/PMC4840793/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4840793/).

<sup>9</sup> Cf. Hull, Darby. “Reining in the Commercialized Foreign Clinical Trial.” *Journal of Legal Medicine* 36/3-4 (2015): 367-401.

(iii) The growth of the clinical trials market, as well as its globalized dimension, are correlated with amplified regulatory efforts – at national, regional, and international level – as well as with an increased availability of clinical trials data and information. Examples of relatively recent regulatory efforts and best practices include the drafting of the European Union Clinical Trials Regulation, which poses a heightened degree of attention on information sharing in Europe,<sup>10</sup> and the increased accessibility of *the WHO International Clinical Trials Registry Platform and the pervasiveness of clinical trials registration*.<sup>11</sup> In this context, we believe that the *emergence of new sources* favors and requires the development of up-to-date contributions in the field of clinical trials law and policy.

Taking into consideration the three underlying focuses of this thesis, we briefly present the aims of this contribution. First, in general terms, the research behind this thesis attempted to identify some of the risks and opportunities triggered by clinical trials in a globalized clinical research environment, specifically with the goal of providing some insights on how to improve human subjects' protection in clinical trials. Furthermore, the thesis follows two fil rouge: the global dimension of clinical trials and their status and challenges in developing economies *vis a vis* developed economies; and the role that

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<sup>10</sup> 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 (Text with EEA relevance). Further examples of recent regulatory efforts include the national action of some states e.g. India, which is in the process of rendering it mandatory for sponsors and investigators to disclose clinical trials' outcomes (see: Koshy, Jacob. "Call to make clinical trial data public." *The Hindu*, 22 Nov. 2017, [www.thehindu.com/news/national/call-to-make-clinical-trial-data-public/article20667337.ece](http://www.thehindu.com/news/national/call-to-make-clinical-trial-data-public/article20667337.ece)) and the United States, with regard to the implementation of an "electronic system that enables accurate collection of data and promotes data-sharing across multiple clinical trial sites" (see: Commissioner, Office of the. "Advancing Regulatory Science - OneSource Checklists: Tools for Integrating Care and Research and Catalyzing a Sea Change in the Practice of Medicine." U.S. Food and Drug Administration *Home Page, Office of the Commissioner*, [www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm574079.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm574079.htm)). At the international level it is worth noting the discussion currently open on a set of guidelines for multi-regional clinical trials at the level of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (see: "ICH E17 Guideline reaches Step 2b of the ICH Process." *ICH*, [www.ich.org/ichnews/newsroom/read/article/ich-e17-guideline-reaches-step-2b-of-the-ich-process.html](http://www.ich.org/ichnews/newsroom/read/article/ich-e17-guideline-reaches-step-2b-of-the-ich-process.html)).

<sup>11</sup> As of October 2017, 456045 records were accessible for 390098 trials. The difference in the two figures is due to the fact that – as specified in the first page of the ICTRP's search portal – "trials are sometimes recorded in more than one registry. These records can refer to each other using the 'Secondary ID' field. The search portal uses these Secondary IDs to group records about the same trial together in the search results." See: *ICTRP Search Portal*, [apps.who.int/trialsearch/Default.aspx](https://apps.who.int/trialsearch/Default.aspx). To read the number *vis a vis* figures that regard the entity of the registration phenomenon before the introduction of the ICMJE policy note, for example, that before the implementation of the policy ClinicalTrials.gov, the largest trial registry at the time, contained 13,153 trials (see Laine, Christine, et al. "Clinical trial registration—looking back and moving ahead." (2007): 2734-2736).

different stakeholders play in the field of clinical trials in the light of the need to balance their competing interests. Lastly, in order to pursue this research interest, this thesis relies on three different approaches, depending on the issues addressed by each chapter: in some sections it adopts a descriptive approach, to identify the most relevant issues that legislators and private stakeholders currently face or will face in the near future in the field of clinical trials; in some sections it adopts a comparative approach, focusing on the similarities and divergences between regulatory standards applicable to clinical trials in different contexts and jurisdictions; and in some sections it adopts a more practical approach, aimed at the collection and interpretation of first-hand clinical trials data.

Second, more specifically, each of the chapters discuss one or more narrow research questions. As a result, some of the chapters included in this contribution can potentially stand alone, as research papers, while others need to be read as providing information essential for a better understanding of the thesis as a whole. In particular:

(i) Chapter One presents a comprehensive review of the literature relating to the law and policy of clinical trials, with a specific focus on their international dimension. It provides the reader with an introduction to the field of clinical trials-related research and it lays the groundwork for the following chapters, explaining how the research questions raised in this contribution fit into the current stream of clinical trials literature.

(ii) Chapter Two describes the main rights touched upon by the conduction of and participation in clinical trials. The observations developed in this chapter allow readers to better understand the challenges that legislators willing to regulate clinical trials and protect human subjects regularly face (for example *vis a vis* the right to health and right to information discourse).

(iii) Chapter Three describes the main stakeholders involved in clinical trials (human subjects, sponsors, and investigators) and how their interests align or collide in the face of the need to balance three traditional healthcare competing paradigms: access, cost, and quality.

(iv) Chapter Four deals with the concerns raised by the globalization of clinical trials, building on one of the most renowned contributions in the field of clinical trials' ethics

literature by Emanuel et al.<sup>12</sup> The chapter presents concrete legal formulations and examples of implementation of the relevant ethical principles, expanding with the addition of a supplementary ethical principle applicable to international clinical trials.

(v) Chapter Five presents a comparative analysis of the European Union and United States clinical trial legal frameworks. While the chapter adopts a narrow view and focuses on the core legislative provisions applicable in the two jurisdictions, rather than touching also upon the guidance tools provided by local authorities, it nevertheless allows to identify points of contacts and similarities and to detect divergences and differences between the two systems, providing detailed information about the most challenging elements for clinical trials stakeholders.

(vi) Chapter Six focuses on the issue of clinical trials data transparency. The “case for registration” is taken into consideration because the global dimension of the issue is particularly relevant and the development of an international set of standards in this context has been successfully achieved thanks to synergy between different stakeholders. The chapter presents an overview of the competing interests that stand behind the creation of clinical trial registries, of the history and functional characteristics of the principal registries, and some of the challenges that are still unresolved in this context.

(vii) Finally, Chapter Seven adopts a more “practical” approach. It introduces the results of several interviews conducted with clinical trials sponsors, patients’ and consumer organizations, and investigators and presents the findings of a simple empirical analysis focused on recruitment-dynamics, conducted on the basis of a sample of 394 clinical trials. Through its practical approach, the chapter aims at providing up-to-date figures and insights on which clinical trials’ literature and stakeholders may want to rely.

To conclude, through the above-described chapters, this thesis aims at representing an original contribution in the field of clinical trials law and policy at the international level.

In addition to what introduced above, we briefly introduce some potential future research steps and expansions of scope of the research presented in this thesis.

Regarding the comparative analysis introduced in Chapter Five, we plan to expand the research to account for the significant amount of guidance issued by European and United

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<sup>12</sup> Emanuel, Ezekiel J., et al. “What makes clinical research in developing countries ethical? The benchmarks of ethical research.” *The Journal of Infectious Diseases* 189.5 (2004): 930-937.

States authorities, which often contribute to increase the proximity of the two legal systems in the field of clinical trials. Depending on the timeline of the European Union Clinical Trials Regulation's implementation, as well as on the political challenges that may impact it in some parts of Europe (that is, e.g.: Brexit), the research may need to be expanded to take into account further fragmentation and divergences at the European level. In addition, we expect that, in the long term, the comparative approach adopted in Chapter Five could be applied also to other jurisdictions as well as to joint/international regulatory efforts (such as those promoted in the context of the International Council for Harmonisation).

In line with the above, we also plan to run an updated empirical analysis, building on the one introduced in Chapter Seven. Based on a series of scoping searches conducted following the thesis defense, we expect the updated empirical analysis to reflect the most recent dynamics in the field of international clinical trials, including an increased reliance on international clinical trials and the popularity of certain jurisdictions as clinical trials hosts. A further research step, in relation to this topic, could entail assessing the result of the empirical analysis in light of the most relevant regulatory choices made by each jurisdiction (e.g., in terms of clinical trials data transparency obligations, marketing authorization application requirements, informed consent standards, and post-marketing pharmacovigilance duties). This research angle could allow to establish to what extent regulatory challenges and opportunities might have influenced the choices of the relevant clinical trials stakeholders in each jurisdiction.

## **CHAPTER ONE: REVIEW OF THE LITERATURE**

### *I. Introduction*

This chapter will present a comprehensive review of the literature in the field of law and policy relating to clinical trials. Its scope is a double-sided one: on the one hand, to provide the reader with an introduction to the field of clinical trials-related research; on the other hand, to lay the groundwork for the following chapters, explaining how the research questions raised in this contribution fit into the current stream of clinical trials literature.

As the field of clinical trials research is a niche one – especially when the focus of the research touches upon law and policy – the literature is not extremely vast. Nevertheless, this chapter attempts to present and organize it. In order to do so, it refers to legal-political as well as medical-pharmaceutical contributions.

The following paragraphs will define the topic under consideration, will draw a picture of the most relevant approaches and contributions in the field, and will finally present some conclusions.

### *II. Preliminary Notes*

First, this review focuses on the literature produced on the conduction and regulation of clinical trials with an international dimension and connotation. It should be noted at this juncture that the term “international dimension” is used here to indicate any clinical trial involving sponsors, investigators, and/or human subjects originally based in a variety of States. Furthermore, the definition of “clinical trial” upon which this chapter is built, is that provided by the World Health Organization (hereinafter, WHO). The latter deems the concept of clinical trials to comprise “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.”<sup>13</sup>

Second, four identifiable strands of literature can be identified in the research devoted to clinical trials with an international dimension. The structure of this chapter reflects such

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<sup>13</sup> “Clinical trials.” *WHO*, World Health Organization (2017) [www.who.int/topics/clinical\\_trials/en/](http://www.who.int/topics/clinical_trials/en/).

consideration, despite the fact that many of the issues that each strand touches upon are common and overlapping. Each strand can be identified on the basis of its focus. The four strands, therefore, can be seen to adopt: (i) the description as the focus; (ii) ethics and law as the focus; (iii) identity as the focus; and (iv) geography as the focus. The general interest in providing the audience with insights and inputs regarding the scope of a reform of the current clinical trials legal regime is the *fil rouge* that bounds the four approaches – especially (ii)-(iv) – within this contribution.

### III. Strands of Literature

The following paragraphs will present the principal contributions developed within each of the four strands described above.

#### *(1) Description as the Focus*

The first strand relies on the description of clinical trials as the focus of its research. This strand is the most technical in nature, and includes all of the literature produced with the aim of describing how clinical trials work and how they are structured when they adopt an international dimension. It comprises a mixture of legal-political and medical-pharmaceutical literature. It can be deemed relevant for the scope of this contribution, to the extent that it provides reliable figures in terms of e.g. the number of clinical trials conducted in the past decades, percentages of clinical trials conducted with an international dimension, and the nature and incidence of any risk factor involved in the organization of clinical trials, whether they are being conducted in an exclusively local or in an international dimension.

#### *(2) Ethics and the Law as the Focus*

The second strand of clinical trials literature identified here has ethics and the law as its focus. The literature produced in this context can be seen as dealing with four sub-strands: (a) morality; (b) binding legal instruments; (c) other regulatory tools; and (d) the outcomes of existing litigation.

(a) With regard to *morality*, the contributions that belong to the first sub-strand tend to observe the regulation of clinical trials (or lack thereof) as a choice with deep moral implications. They trace aspects of the regulation and conducting of clinical trials that are not legal *per se*, but that precede or accompany the legal choices taken in the field. The concern conveyed by some of the contributions that fall within this field regards the

risk that clinical trials conducted “abroad” – in particular, when sponsors based in developed economies recruit investigators and human subjects in developing economies – pose in terms of “colonialism”. The latter term is used, for example, by Treadaway to describe the issues that arise when a population that is vulnerable both in terms of access to healthcare and economic resources is recruited by sponsors based in developed countries to serve as clinical trial participants in developing countries.<sup>14</sup> As Fidler – exploring the “geographic morality” of clinical trials – aptly described, authors that focus on the moral implications of clinical trials tend to join one of three approaches borrowed from the international relations discourse: realism, where morality is not deemed to have a role in the relations among States;<sup>15</sup> rationalism, where States can structure their relations according to common moral grounds to pursue peaceful relations;<sup>16</sup> and, finally, revolutionism, where international relations are seen as the means for achieving the unity – even the moral one – of mankind.<sup>17</sup>

(b) The second sub-strand comprises one of the most relevant genres for this contribution, and focuses on the study of the *legal instruments* that regulate clinical trials. Traditionally, literature belonging to this category considers legal certainty as a value.<sup>18</sup> It entails one of the following aims: (i) to describe purely national legislation, especially that which aims at informing practitioners in the field of clinical trials or advocating for reforms of such national legislation. For example, Brunts and Rusczek focused on the United States (US) regulation of clinical trials and covered its implications in different fields of their national law, including civil liability and commercial litigation.<sup>19</sup> (ii) To describe the relevant international legal instruments, once again with the purpose of informing practitioners and/or advocating for reforms, as undertaken, for example, by Traynor.<sup>20</sup> Finally, (iii) comparing existing legal instruments, to facilitate the

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<sup>14</sup> Treadaway, Lauren. “Big Pharma’s Heart of Darkness: The Alien Tort Statute and Preventing Clinical Trial Colonialism.” *Georgetown Journal of International Law* 43 (2011): 1419.

<sup>15</sup> Fidler, David P. “Geographical Morality Revisited: International Relations, International Law, and the Controversy over Placebo-Controlled HIV Clinical Trials in Developing Countries.” *Harvard International Law Journal* 42.2 (2001): 316-320.

<sup>16</sup> *Ibid.*

<sup>17</sup> *Ibid.*

<sup>18</sup> Cf. Treadaway, *op. cit.*

<sup>19</sup> Brunts, Hermes and Andrew P. Rusczek. “The International Clinical Trials Roadmap: Steering Clear of Legal and Practical Roadblocks.” *Journal of Health & Life Sciences Law* 5.3 (2012): 1.

<sup>20</sup> Traynor, Michael, “Emerging Issues Regarding Globalization of Pharmaceutical Research, Insurance, Informed Consent, Securities Litigation, and Public Policy.” written for *ALI-ABA, Emerging Issues in*

interpretative exercise of the subjects that conduct clinical trials in more than one State and/or to assess the feasibility of a harmonization of the applicable legal standards. Notably, one of the most developed comparative approaches focuses on the divergences and similarities between the legislation in force in the US and that in force in the European Union (EU). This is the case of the contributions developed, among others, by Trubek, Westergren, and Choi.<sup>21</sup>

(c) The third sub-strand is often blended with the second and analyzes all of the relevant *sources* in the field of clinical trials regulation; however, these are not strictly binding on states and private stakeholders. In practical terms, this sub-strand deals with the regulatory tools produced by non-governmental actors or by States (yet without a compelling legal value). An exemplary tool observed in this field is the Nuremberg Code, central in Shtilman's contribution.<sup>22</sup> The literature produced in this context has a peculiar value, as it often provides insights on the work and opinion of working groups that represent sponsors and investigators, and that may serve as basis for prospective legislative reforms. For example, Malinowski, and Gautreaux have engaged in the description of a well-known law and policy reform proposal.<sup>23</sup>

(d) Finally, the fourth sub-strand aims at discerning the outcome of existing litigation. While litigation that regards clinical trials – both at national and international level – is not particularly developed in all legal systems, relevant cases have emerged in the past years. Studying their procedural and substantive aspects offers a chance to test national and international norms in the field. This has been, for example, one of the focuses of Treadaway's research.<sup>24</sup> The literature that focuses on such litigation provides insights in

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*Biotechnology Law* (2007) accessed on *LexisNexis*, [www.lexisnexis.com/](http://www.lexisnexis.com/) (Lexis reference: SN014 ALI-ABA 73).

<sup>21</sup> Respectively, Trubek, Louise, et al. "Improving Cancer Outcomes through Strong Networks and Regulatory Frameworks: Lessons from the United States and the European Union." *Journal of Health Care Law & Policy* 14 (2011): 119. Westergren, Amy. "The Data Liberation Movement: Regulation of Clinical Trial Data Sharing in the European Union and the United States." *Houston J. Int'l L.* 38.3 (2016). And Choi, Rebecca. "Increasing Transparency of Clinical Trial Data in the United States and the European Union." *Washington University Global Studies Law Review* 14 (2015): 521.

<sup>22</sup> Shtilman, Yevgenia. "Pharmaceutical Drug Testing in the Former Soviet Union: Contract Research Organizations as Broker-Dealers in an Emerging Testing Ground for America's Big Pharma." *Boston College Third World Law Journal* 29 (2009): 425.

<sup>23</sup> Malinowski, Michael J., and Grant G. Gautreaux. "All That is Gold Does Not Glitter in Human Clinical Research: A Law-Policy Proposal to Brighten the Global Gold Standard for Drug Research and Development." *Cornell International Law Journal* 45 (2013): 185.

<sup>24</sup> Treadaway, *op. cit.*

terms of the susceptibility of wrongdoings to redress in the field of clinical trials, and, despite its specific nature, provides the reader with important elements of analysis, especially to the extent that it highlights the operational virtues and vices of current regulatory regimes.

In sum, authors that pose ethics as core of their analysis tend to it to take a stand in the debate over the morality of clinical trials – especially when they have an international dimension – to analyze the way in which clinical trials are regulated both through binding legal provisions and through other soft-law tools, and/or to study the shape that clinical trials-related litigation has taken in recent times.

### *(3) Identity as the Focus*

The third strand of literature presented here focuses on the identity – but also the interests and concerns – of the actors involved in clinical trials (especially those conducted with an international dimension). In this context, regulating clinical trials means finding the optimal balance between the interests and concerns of three main stakeholders: patients/participants (i.e. the human subjects that take part in clinical trials), investigators, and sponsors.

Many authors focus on those “players”, while maintaining a balanced approach, and aim at describing the interests that belong to each category, as Bard has done in drawing her “taxonomy” of clinical trials’ dynamics.<sup>25</sup> Other authors tend to focus on a single category and to advocate for the prevalence of its particular interests; for example, Hathaway’s work is centered on the decisional and precautionary steps that sponsors and investigators willing to conduct clinical trials in a third country ought to consider.<sup>26</sup> With regard to contributions to clinical trials literature that advocate for the promotion of a specific goal – which often corresponds to the interest of one category of stakeholders – the case for or against the goal of centralizing clinical trials registration is worth observing. Contributions developed to support the creation and implementation of centralized clinical trials registries – such as the work of Galbraith, Francer and Turner,

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<sup>25</sup> Bard, Jennifer S. “A Taxonomy for Analyzing Legal and Ethical Issues Arising When Conducting Human Subject Research Outside the Borders of One’s Own Country.” *Houston Journal of International Law* 37 (2015): 1. And Hathaway, Carolyn R., et al. “Looking Abroad: Clinical Drug Trials.” *Food and Drug Law Journal* 63. 3 (2008): 673.

<sup>26</sup> E.g. as a case of study that advocates for an increased role of integrated networks of doctors, patients, and hospitals: Trubek, *op. cit.*

and Cohen et al. – tend to be grounded in the idea that they contribute to the empowerment of patients and increase the quality of and lack of biases in clinical trials’ results.<sup>27</sup>

In general terms, the following are some of the issues that are commonly presented as grey areas at the intersection of the interests of the three main stakeholders: the existence and scope of a right to access to treatments – often declined in terms of right to health, right to life, and clinical trials’ as public goods;<sup>28</sup> the existence and scope of a right to information – often analyzed within the debate over the creation and enforcement of centralized (i.e. supra-national) clinical trials registries or within the debate over the nature and content of the participants’ informed consent;<sup>29</sup> the legality and scope of placebo clinical trials;<sup>30</sup> and the existence and scope of a right to the so called “Best Proven Diagnostic and Therapeutic Method” (i.e. best available treatment).<sup>31</sup>

#### *(4) Geography as the Focus*

The fourth and final identifiable strand of literature relies on geography as its focus. Similarly to the third strand, it allows authors to structure their research in terms of potentially conflicting interests and categories of actors. However, while in the third strand, the factor that sets “players” apart is the role that they play in the organization and carrying out of clinical trials, in the fourth strand, geography constitutes the discerning factor.

In particular, authors active in this field tend to focus their research on one or more of the following objects – either adopting a descriptive *super partes* approach or advocating

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<sup>27</sup> Respectively, Galbraith, Christine D. “Dying to Know: a Demand for Genuine Public Access to Clinical Trial Results Data.” *Mississippi Law Journal* 78 (2008): 705. Jeffrey K. Francer and Natalie A. Turner. “Responsible Clinical Trial Data Sharing: Medical Advancement, Patient Privacy, and Incentives to Invest in Research.” *Journal of Health & Life Sciences Law* 8.1 (2014): 63. And Cohen, Katherine et al. “Predictable Materiality: A Need for Common Criteria Governing the Disclosure of Clinical Trial Results by Publicity-Traded Pharmaceutical Companies.” *Journal of Contemporary Health Law and Policy* 29 (2012): 201.

<sup>28</sup> E.g. Lemmens, Trudo, and Candice Telfer. “Access to Information and the Right to Health: the Human Rights Case for Clinical Trials Transparency.” *American Journal of Law and Medicine* 38 (2012): 63.

<sup>29</sup> E.g. Doherty, Joan M. “Form over Substance: The Inadequacy of Informed Consent and Ethical Review for Thai Injection Drug Users Enrolled in HIV Vaccine Trials.” *Pacific Rim Law & Policy Journal* 15.1 (2006): 101. And McGregor, Molly. “Uninformed Consent: The United Nations’ Failure to Appropriately Police Clinical Trials in Developing Nations.” *Suffolk Transnational Law Review* 31/1 (2007): 103.

<sup>30</sup> Fidler, *op. cit.*

<sup>31</sup> Shtilman, *op. cit.*

for the centrality of the role of one of them: single States belonging to the category of developed economies, single States belonging to the category of developing economies or economies in transition, and/or clusters of States and international organizations. For example, contributions that belong to this strand have been developed by Schuster and Ourso.<sup>32</sup> The allegation that the interests of different States can be described on the basis of a line dividing developed and developing economies is not free from controversies.<sup>33</sup> However, while admittedly, it should not be seen as a clear-cut line, in the context of clinical trials regulation, it may become relevant to the extent that it allows for a more precise identification of the interests and concerns of different legislators and “prospective legislators” on the international scenario. In particular, it provides for a chance to not underestimate the need for measures tailored to the risks and opportunities that in the case of developed and developing economies have different shades.

Sub-issues addressed in this context overlap with those addressed by the literature which adopts an ethical focus. For example, they regard concerns for the scarce efficacy of the inspection-procedures in place in host-States, the increased risks of fraud and abuse in certain States, as well as of the risk of exploitation of vulnerable populations.<sup>34</sup>

#### IV. Preliminary Conclusions

To conclude, the literature produced in the field of clinical trials regulation and specifically with a focus on clinical trials that adopt an international dimension is highly specific and often fragmented. Nevertheless, four – often overlapping – focuses can be identified, and will be taken into consideration in the following chapters of this thesis. Namely, the approach that focuses on a descriptive analysis, that which focuses on ethical and purely legal aspects of clinical trials, that which focuses on the identity and interests of the stakeholders involved in the conduction of each clinical trial, and, finally, that

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<sup>32</sup> Schuster, Breanne M. “For the Love of Drugs: Using Pharmaceutical Clinical Trials Abroad to Profit Off the Poor.” *Seattle Journal for Social Justice* 13 (2014): 1015. And Ourso, Andre. “Can the FDA Improve Oversight of Foreign Clinical Trials: Closing the Information Gap and Moving Towards a Globalized Regulatory Scheme.” *Annals of Health Law* 21 (2012): 493.

<sup>33</sup> While authors often do not describe on the basis of which criteria they distinguish the two categories, within this contribution the categorization provided by the UN, *World Economic Situation and Prospects 2017* (New York, 2017) 153-154, will be relied on.

<sup>34</sup> Schuster, *op. cit.* and McGregor, *op. cit.*

which focuses on the – sometimes divergent – interests of the States involved in the regulation of clinical trials.

This thesis aims at providing a set of specific contributions in the context of several of the strands of literature described above. For example, it will present an analysis of the major rights involved in clinical trials regulation, a discussion of clinical trials ethics in context, and updated comparative analysis of the existing legal instruments in force at the national level in the US and the EU – an exercise that belongs to the second strand identified here; and an analysis of the interaction between the interests of different stakeholders involved in clinical trials – which belongs to the third strand identified here. Incidentally, it will provide an empirical analysis focusing on the international dimension of clinical trials and its prevalence in the case of some countries' action – which belongs to the fourth strand identified here.

## **CHAPTER TWO: THE PROTECTION OF HUMAN SUBJECTS IN CLINICAL TRIALS – RELEVANT ISSUES IN THE RIGHT TO HEALTH AND RIGHT TO INFORMATION DISCOURSES**

### **I. Introduction**

This chapter will describe the main rights touched upon by the carrying out of and participation in clinical trials. In general, the observations developed in this chapter can be seen as essential to allowing readers to better understand the challenges faced by legislators willing to regulate clinical trials and protect human subjects. Furthermore, the identification and analysis of such rights and of some of their principal practical applications and implications is propaedeutic to the development of other chapters in this thesis.

In particular, this chapter provides notions relevant for the understanding: (i) of the contribution on the three competing paradigms in clinical trials policy and legislation – access, quality, and cost;<sup>35</sup> (ii) of the ethical considerations upon which this thesis relies;<sup>36</sup> and (iii) of the elements that are at the core of the comparative analysis presented herein.<sup>37</sup> In particular, the second section of this chapter will revolve around the right to health discourse, while the third will revolve around the right to information discourse.

### **II. Right to Health**

Discussing clinical trials regulation in the context of international law and, specifically, the protection of human subjects entails the opening of a dialogue concerning the nature and scope of the right to health. Therefore, this section will provide the reader with some introductory notions in terms of definition, legal sources, and the nature of the right to health. It will then move to discuss the implications of the right to health in the context of clinical trials policy and regulation touching upon a series of specific issues – including the issue of sample tailoring, subject recruitment, placebo-controlled clinical trials, and standards of care.

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<sup>35</sup> See Chapter III in this thesis.

<sup>36</sup> See Chapter IV in this thesis.

<sup>37</sup> See Chapter V in this thesis.

*(1) The Right to Health: Introductory Notions*

The nature and scope of the right to health is the object of a flourishing literature, both within the borders of single countries – be they developed or developing economies – and in the general international law and policy discourse.<sup>38</sup> First, with regard to the definitional issue, it is worth noting that there seems to be a widespread consensus concerning the core elements in the definition of the right to health. The latter consists of the enjoyment of a certain standard of health. Where this standard ought to be placed, who the institutional subject in charge of establishing it is, and towards which audience, remain arguments of debate among researchers.<sup>39</sup> Some insights, however, can be derived from the interpretation of both international legal instruments and comparative studies that focus on state practice. In general, in terms of international law, there are two main sources that are relevant with regard to the right to health: obligations deriving from international legal instruments and those deriving from customary international law.

The most relevant international legal instruments that directly or indirectly refer to the right to health are: the WHO Constitution, which touches upon it in its Preamble (Preamble), stating that “[t]he enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social conditions”;<sup>40</sup> the International Covenant on Economic, Social and Cultural Rights which at Article 12 (1) affirms that “[t]he States Parties to the present Covenant recognize the right of everyone to the enjoyment of the highest attainable standard of physical and mental health”;<sup>41</sup> the United Nations Convention on the Rights of the Child, which at Article 24 (1) states that “States Parties recognize the right of the child to the enjoyment of the highest attainable standard of

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<sup>38</sup> See e.g. Farmer, Paul. “Pathologies of Power: Rethinking Health and Human Rights.” *American Journal of Public Health* 89.10 (1999): 1486-1496. Sen, Amartya. “Why and How is Health a Human Right?” *The Lancet* 372.9655 (2008): 2010. And Leary, Virginia A. “The Right to Health in International Human Rights Law.” *Health and Human Rights* 1.1 (1994): 24-56 and the contributions cited in the following footnotes.

<sup>39</sup> Cf. Toebes, Brigit. “The Right to Health as a Human Right in International Law.” *Refugee Survey Quarterly* 20.3 (2001). And Mann, Johnathan. “Health and Human Rights.” *American Journal of Public Health* 96.11 (2006).

<sup>40</sup> *Constitution of the World Health Organization* (Geneva: World Health Organization, 1948).

<sup>41</sup> Article 12 (1), UN General Assembly, *International Covenant on Economic, Social and Cultural Rights*, 16 December 1966, United Nations, Treaty Series, vol. 993, p. 3.

health”;<sup>42</sup> and the Convention on the Elimination of All Forms of Racial Discrimination, which at Article 5 (e)(iv) provides that States Parties undertake to prohibit and eliminate racial discrimination in the enjoyment of “the right to public health, medical care, social security and social services.”<sup>43</sup>

As of today, 194 States have ratified the United Nations (UN) Convention on the Rights of the Child,<sup>44</sup> 177 States have ratified the International Convention on the Elimination of All Forms of Racial Discrimination,<sup>45</sup> and 164 States have ratified the International Covenant on Economic, Social and Cultural Rights.<sup>46</sup>

As can be noted by the wording of the abovementioned provisions, the most common term used to refer to the standard of health which is to be promoted by States is the “highest.” With regard to the customary nature of the right, as it is well known, customary international law can be identified on the basis of a two-prong test under which two elements are to be assessed: *opinio iuris* and state practice.<sup>47</sup> In the context of the right to health, Kinney has provided a comprehensive study of the customary nature of the right, noting that, as of 2000, 83 states had ratified at least a regional treaty acknowledging the right to health, and 109 had recognized it in their own constitution.<sup>48</sup> Backman et al. have developed a study of national approaches and standards to the right to health, assessing its status in 194 countries.<sup>49</sup> Despite the availability of such data,

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<sup>42</sup> Article 24 (1), UN General Assembly, *Convention on the Rights of the Child*, 20 November 1989, United Nations, Treaty Series, vol. 1577, p. 3.

<sup>43</sup> Article 5(e)(iv), UN General Assembly, *International Convention on the Elimination of All Forms of Racial Discrimination*, 21 December 1965, United Nations, Treaty Series, vol. 660, p. 195.

<sup>44</sup> UN, UN Treaty Collection.

[https://treaties.un.org/pages/viewdetails.aspx?src=ind&mtmsg\\_no=iv-11&chapter=4&clang=\\_en](https://treaties.un.org/pages/viewdetails.aspx?src=ind&mtmsg_no=iv-11&chapter=4&clang=_en).

<sup>45</sup> UN, UN Treaty Collection.

[https://treaties.un.org/Pages/ViewDetails.aspx?src=IND&mtmsg\\_no=IV-2&chapter=4&clang=\\_en](https://treaties.un.org/Pages/ViewDetails.aspx?src=IND&mtmsg_no=IV-2&chapter=4&clang=_en).

<sup>46</sup> UN, UN Treaty Collection.

[https://treaties.un.org/Pages/ViewDetails.aspx?src=IND&mtmsg\\_no=IV-3&chapter=4&clang=\\_en](https://treaties.un.org/Pages/ViewDetails.aspx?src=IND&mtmsg_no=IV-3&chapter=4&clang=_en).

Additionally, it is worth recalling that the 1948 Universal Declaration of Human Rights, at Article 25, reads: “Everyone has the right to a standard of living adequate for the health and well-being of himself and his family, including (...) medical care.” Article 25, UN General Assembly, *Universal Declaration of Human Rights* (Paris, United Nations, 1948).

<sup>47</sup> Malcom N. Shaw, *International Law*, 7<sup>th</sup> edition (Cambridge University Press, 2014).

<sup>48</sup> Kinney, Eleanor D. “The International Human Right to Health: What Does This Mean for Our Nation and World.” *Indiana Law Review* 34 (2000): 1457-1465.

<sup>49</sup> Backman, Gunilla et al. “Health Systems and the Right to Health: an Assessment of 194 Countries.” *The Lancet* 372/9655 (2008): 2047-2085.

attributing a customary value to the right to health is not an exercise free of challenges, but ultimately the right-to-health provisions included in the ICESCR can be deemed to be customary in nature, or at least at the core thereof.<sup>50</sup> With regard to the challenges to the enforceability of the right to health, Backman et al. suggested that “[c]ountries have a legal obligation to progressively realise the right to the highest attainable standard of health and therefore to improve their health systems progressively.”<sup>51</sup>

In this context, two main challenges follow the life of the right to health: First, both “highest” and “progressively” remain subjective standards as far as States have different political attitudes and preferences as well as unequal stages of economic development, and face a variety of challenges in terms threats to the health of their citizens. Second, consequently and in any event, implementation and enforcement challenges remain extremely complex; not only because they depend on the definition of the right but also because they are complicated by the absence of a clear chain of responsibilities.

General Comment 14 presents the UN Committee on Economic, Social, and Cultural Rights’ interpretation of Article 12 of the International Covenant on Economic, Social, and Cultural Rights and helps to partially clarify those issues.<sup>52</sup> Despite its lack of binding force, it represents a reliable and authoritative source. Two key findings built into the Comment are the following: core obligations are not subject to progressive realization and resource availability, and States “have an obligation to ensure that their actions as members of international organizations take due account of the right to health”. As of the role of supra-national institutions, a strand of literature has developed over time to address the challenges which the WHO, as an international organization entrusted with the aim of promoting global health, faces.<sup>53</sup>

This chapter does not aim at solving the dilemma over the legal nature of the right to health; rather, it agrees with Fidler’s intuition that “[n]either international law nor global

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<sup>50</sup> Kinney, *op. cit.*

<sup>51</sup> Backman, *op. cit.*

<sup>52</sup> Committee on Economic, Social and Cultural Rights, *General Comment No. 14: The Right to the Highest Attainable Standard of Health (Art. 12)*, (UN Committee on Economic, Social and Cultural Rights, Twenty-second session, 2000), U.N. Doc. E/C.12/2000/4 (2000), reprinted in *Compilation of General Comments and General Recommendations Adopted by Human Rights Treaty Bodies* (U.N. Doc. HRI/GEN/1/Rev.6, 2003): 85.

<sup>53</sup> Cf. Taylor, Allyn Lise. “Making the World Health Organization Work: a Legal Framework for Universal Access to the Conditions for Health.” *American Journal of Law and Medicine* 18.4 (1992): 301.

health jurisprudence provides a magic bullet against the public health problems in the world today.”<sup>54</sup> Nevertheless, it aims at providing readers with some insights into the connections between the right to health and the conduction and regulation of clinical trials at the international level. It also aims at contributing to structuring a discussion that is still considered underdeveloped.<sup>55</sup> In this sense, it seems pragmatic to follow the path chosen by other authors, such as Kinney herself. The latter suggested that “[d]efining the content of a right to health is a formidable challenge. But the challenge should not impede the recognition and development of a human right to health in international human rights law.”<sup>56</sup> This observation is particularly apposite in the context of clinical trials in which the concreteness of the matter often makes it easier to understand which choices a legislator – being it a national or an international one – is facing. Hence, to overcome the risks associated with tackling the definitional challenges of the right to health and while keeping the formulation that international provisions have given it over time, the next paragraphs will focus on its aspects “in the field” (of clinical trials).

## *(2) Right to Health in the Context of Clinical Trials*

The discourse on the existence, nature, and scope of the right to health meets the interests and concerns of clinical trials policy and regulation in two specific respects. The first regards the dichotomy right-duty to participate and tailored access: a case of balancing public and private interests in restricting or promoting access to clinical trials *vis-à-vis* the costs – both in terms of public health and material monetary costs – and effects on quality of the results of such restrictions and promotions. The second is potentially the more challenging and specific issue, and concerns the use of placebo-controlled studies and the role of local standards of care.

### *(a) The Dichotomy Right-Duty to Participate: Sampling and Tailoring in Clinical Trials*

This section will address three sources of concern in the context of the right to health and clinical trials: small samples, coercion, and over- or underrepresentation of certain portions of the population. The acknowledgment that they must be addressed in the debate concerning the regulation of clinical trials should ensure that legislators and the

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<sup>54</sup> Fidler, David P. “International Law and Global Public Health.” *Kansas Law Review* 48 (1999): 1.

<sup>55</sup> Cf. Lemmens, and Telfer, *op. cit.*

<sup>56</sup> Kinney, *op. cit.*

stakeholders involved will not underestimate the risk and opportunities connected with such issues.

First of all, in general, and especially in case of potentially life-saving protocols, many patients advocate for increased access to clinical trials as a declination of their right to health (and access to healthcare). For example, a strand of service-industry has developed to favor patients' access to clinical trials, Flatiron being one of the leading companies in the field.<sup>57</sup> The patients' motivation is clear and is often coupled with the feeling that they are not provided with the opportunity to participate due to their lack of information.<sup>58</sup> While the issues connected with the right to information will be addressed later in this chapter, it can preliminarily be noted that a trade-off between costs (either public or private) and access to clinical trials exists. In particular, this seems to be one of the issues on which sponsors and legislators are aligned: there would be no point in enlarging samples of participants beyond what needed for scientific purposes. This would merely increase the cost for sponsors and put at risk a larger sample of patients, in case of unsuccessful protocols. In fact, limitations on the size of the samples are one of the key considerations in clinical trials planning as sample size estimation and the need to avoid over- and under-estimation are extremely important in the development of solid clinical trials.<sup>59</sup> As a result, clinical trials conducted on *small samples* are increasingly popular as – while they may be seen as restricting access to participants willing to take part in the studies – they present procedural advantages in terms of enrollment, review of records, and timing.<sup>60</sup> One aspect that makes them particularly attractive for investigators and sponsors is that they require the participation of few centers, and this makes it easier to obtain ethical and institutional approval.<sup>61</sup>

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<sup>57</sup> Flatiron, *Flatiron Health*, [www.flatiron.com](http://www.flatiron.com). See also Abernethy, Amy and Sean Khozin. "Clinical Drug Trials May Be Coming to Your Doctor's Office." *The Wall Street Journal* (12 Sept. 2017)

[www.wsj.com/articles/clinical-drug-trials-may-be-coming-to-your-doctors-office-1505256988](http://www.wsj.com/articles/clinical-drug-trials-may-be-coming-to-your-doctors-office-1505256988).

<sup>58</sup> Ibid.

<sup>59</sup> Sakpal, Tushar. "Sample Size Estimation in Clinical Trial." *Perspectives in Clinical Research* 1.2 (2010): 67.

<sup>60</sup> Hackshaw, Allan. "Small Studies: Strengths and Limitations." *European Respiratory Journal* 32 (2008): 1141-1143.

<sup>61</sup> Ibid.

On the opposite spectrum of the right to health-related concerns are the clinical trials that potential participants may see as unattractive, and the clinical trials that, by design, would benefit from a better-tailored sample.

The first issue is connected with the existence of a potential “duty to participate” in clinical trials.<sup>62</sup> While enrollment in clinical trials has a deeply voluntary basis, as noted by Spencer B. King, “[n]ot every trial is worthy of patients’ and physicians’ duty to participate. Some trials have little game-changing potential and are designed to support minor changes in the approval of devices, procedures, or therapies.”<sup>63</sup> While *per se* this concern belongs to investigators, it enters the realm of regulation, to the extent that recruitment strategies cross the line between incentives and *coercion* (or undue influence). Financial incentives are common in clinical trials recruitment but they increase the concerns that they may assume a coercive nature directed at people who have limited financial resources.<sup>64</sup> Strategies to overcome that risk encompass the general goal to “improve the effectiveness of methods for informing prospective research volunteers about experimental studies, thereby enhancing the protection of their interests”<sup>65</sup> and specific provisions dedicated to mandatory reviewing by ethical boards and training sessions for recruitment professionals.<sup>66</sup>

The second issue regards the composition of the sample, namely the characteristics of the participants in the clinical trial. According to Caplan and Friesen, in the case of clinical trials conducted in the US, minorities tend to be overrepresented in Phase I studies – where risks are higher and the likelihood of benefits is lower, compared to more advanced trials – and underrepresented in Phase II studies and Phase III trials.<sup>67</sup> Similar

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<sup>62</sup> Schaefer, G. Owen et al. “The Obligation to Participate in Biomedical Research.” *Journal of the American Medical Association* 302/1 (2009): 67-72. And Spencer, B. King III, “Is Participation in Clinical Research a Duty?.” *Journal of the American College of Cardiology: Cardiovascular Interventions* 7.4 (2014): 450.

<sup>63</sup> Spencer, *ibid.*

<sup>64</sup> Groth, Susan W. “Honorarium or Coercion: Use of Incentives for Participants in Clinical Research.” *Journal of the New York State Nurses’ Association* 41.1 (2010): 11.

<sup>65</sup> Lavori, Philip W., et al. “Improving Informed Consent in Clinical Trials: a Duty to Experiment.” *Controlled Clinical Trials* 20.2 (1999): 187-193.

<sup>66</sup> Groth, *op. cit.*, 11.

<sup>67</sup> Caplan, Arthur, and Phoebe Friesen. “Health Disparities and Clinical Trial Recruitment: Is There a Duty to Tweet?” *Public Library of Science Biology* 15.3 (2017). See also Hussain-Gambles, Mahvash, et al. “Why Ethnic Minority Groups are Under-Represented in Clinical Trials: a Review of the Literature.” *Health & Social Care In The Community* 12/5 (2004): 382-388. For specific conditions, see: Heiat, Asefeh, et al. “Representation of the Elderly, Women, and Minorities in Heart Failure Clinical Trials.”

concerns apply to the participation of women.<sup>68</sup> In both cases, there is a widespread agreement circa the benefits of a better-tailored access to clinical trials: samples of high quality (in terms of representation of the population) will guarantee that results will be more easily generalized and therefore used to produce an outcome more beneficial for the general public. Good tailoring of the samples, in this context, represents a bridge between the goals of access and quality in clinical trials. In particular, as noted by Murthy et al., “appropriate” representation of specific patient subpopulations is “necessary to further understanding of race/ethnicity–based differences in presentation, prognosis, and response to therapy.”<sup>69</sup> In response to such concerns, for example, the US Congress has implemented measures to foster a more diverse participation.<sup>70</sup> Unfortunately, those provisions have not conclusively proven to be effective. In fact, while enrollment in clinical trials in the US has grown by almost 50% between 1996 and 2002, the proportion of minorities, women, and elders has declined.<sup>71</sup> Nowadays, potential strategies to foster the access of *underrepresented portions of the population* and build more “participant-friendly” trials include establishing community partnerships, designing study protocols based on the knowledge of participants’ life context, and representing diverse populations in the members of research teams.<sup>72</sup>

In sum, it seems clear that if a clear-cut line can be drawn, it is between well- and badly-designed and conducted trials. In this context, well-designed regulation – to the extent that it can foster well-designed trials – can do much. The common goal and compass in terms of balance of interests should not be increasing access to clinical trials in

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*Archives of Internal Medicine* 162/15 (2002) and El-Sadr, Wafaa, and Linnea Capps. “The Challenge of Minority Recruitment in Clinical Trials for AIDS.” *Journal of the American Medical Association* 267/7 (1992): 954-957.

<sup>68</sup> Cf. e.g. Gurwitz, Jerry H., et al. “The Exclusion of the Elderly and Women from Clinical Trials in Acute Myocardial Infarction.” *Journal of the American Medical Association* 268.11 (1992): 1417-1422. And Heiat, Asefeh, et al., *op. cit.*

<sup>69</sup> Murthy, Vivek H., et al. “Participation in Cancer Clinical Trials: Race-, Sex-, and Age-Based Disparities.” *Journal of the American Medical Association* 29.22 (2004): 2720-2726.

<sup>70</sup> US Congress, National Institutes of Health Revitalization Act of 1993. Subtitle B – Clinical Research Equity Regarding Women and Minorities (1993) sections 131-133.

<sup>71</sup> Murthy, et al., *op. cit.*

<sup>72</sup> The three strategies are discussed in Killien, Marcia, et al. “Involving Minority and Underrepresented Women in Clinical Trials: the National Centers of Excellence in Women’s Health.” *Journal of Women’s Health & Gender-Based Medicine* 9.10 (2000): 1061-1070. The term “participant-friendly” has been introduced by Swanson, G. Marie, and Amy J. Ward. “Recruiting Minorities into Clinical Trials toward a Participant-Friendly System.” *Journal of the National Cancer Institute* 87.23 (1995): 1747-1759.

quantitative terms (i.e. enlarging the pool of patients that they actually involve), rather increasing access to clinical trials in qualitative terms.

Therefore, while regulating clinical trials, legislators should: in general, foster the prospective identification of barriers to enrollment,<sup>73</sup> and, more specifically take into consideration the potential issues connected with sample size estimation, coercion, and under- and over-representation of minorities.

*(b) Placebo-controlled Trials and Local Standards of Care*

In the context of international clinical trials, in addition to the concerns described above, two practices controversially touch upon the right to health: placebo trials and local standards of care. For the subjects that take part in clinical trials, such practices represent two examples of potential trade-offs between access as quality, as they tend to correspond to an increase in access but also to a decrease in term of the quality (or, better, expected quality) of the treatment provided. They are discussed here because they can be seen as belonging to the discourse concerning the right to health, but they are also connected with the quality paradigm (both in terms of quality of care and quality of scientific results) and the cost paradigm (to the extent that placebo trials are deemed to be efficient). Furthermore, they are impregnated with ethical concerns and they represent a few of the issues traditionally addressed by the literature that focuses on the ethics of clinical trials.

As a preliminary note, it should be observed that clinical trials are placebo-controlled when a portion of the participants in the study receive the product that is thereby tested, and a portion of the participants in the study receives a placebo substance.<sup>74</sup> Placebo substances are designed to look like the tested product, in order to prevent participants understanding of which group they belong to, but are made of inert substances such as cellulose or lactose.<sup>75</sup> Alternatively to placebo-controlled trials, investigators may choose

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<sup>73</sup> Cf. Lara Jr, Primo N., et al. “Prospective Evaluation of Cancer Clinical Trial Accrual Patterns: Identifying Potential Barriers to Enrollment.” *Journal of Clinical Oncology* 19.6 (2001): 1728-1733. And Gaspar, Nathalie, and Lorna Fern. “Increasing Access to Clinical Trials and Innovative Therapy for Teenagers and Young Adults with Cancer – A Multiple Stakeholders and Multiple Steps Process.” *Tumors in Adolescents and Young Adults* 43 (2016): 38-49.

<sup>74</sup> Chiodo, Gary T. et al. “Placebo-controlled trials: good science or medical neglect?” *Western Journal of Medicine* 172.4 (2000): 271.

<sup>75</sup> Blease, C. R., et al. “Informed Consent and Clinical Trials: Where Is the Placebo Effect?” *British Medical Journal* (Online) vol. 356 (2017).

to perform active-control trials, meaning trials in which the tested product is compared to the best available treatment.<sup>76</sup>

The general debate surrounding placebo trials revolves around two basic questions: are placebo-controlled trials appropriate, i.e. ethical? And, what are the considerations and actions that can be put in place in order to tackle the risks connected with placebo-controlled trials? These issues have been at the core of many contributions to clinical trials literature.<sup>77</sup> This section of the chapter aims to offer an overview of the risks and opportunities connected with placebo-controlled trials, both in general terms and in the context of international trials. In doing so, it follows two of the core issues identified by Benjamin Freedman et al.<sup>78</sup> – *the existence of harm to subjects, and the role of the Declaration of Helsinki*– but adds one extra element – *the role of local standards of care*, following Angell.<sup>79</sup> In the final paragraph, some considerations connected with regulatory choices will be presented.

First, it is worth acknowledging that placebo-controlled trials carry some risk of harm. Precedents of clinical trials – conducted both in developed economies and developing ones – that produced controversial effects on subjects matched with a placebo treatment exist. Examples of controversial uses of placebo-controlled trials include: the Tuskegee Study of Untreated Syphilis during which, for 40 years, patients affected by syphilis were observed but not administered any treatment, despite the availability of penicillin-based treatments and the lack of the subjects’ informed consent;<sup>80</sup> a placebo-controlled trial of fluphenazine decanoate, which relied on a group of placebo-controlled patients affected by schizophrenia, in which 66 percent of the placebo group relapsed, compared with 8 percent of the treatment group;<sup>81</sup> and several clinical trials on the vertical transmission of human immunodeficiency virus (HIV) infection which took place in developing

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<sup>76</sup> Sławiński, Jacek, and Jerzy Kuźniar. “Clinical Trials: Active Control Versus Placebo – What Is Ethical?” *Science and Engineering Ethics* 10.1 (2004): 73-79.

<sup>77</sup> See e.g. Hill, A. Bradford. “The Continuing Unethical Use of Placebo Controls.” *New England Journal of Medicine* 331.6 (1994): 394-398.

<sup>78</sup> Freedman, Benjamin, et al. “Placebo Orthodoxy in Clinical Research II: Ethical, Legal, and Regulatory Myths.” *The Journal of Law, Medicine & Ethics* 24.3 (1996): 252-259.

<sup>79</sup> Angell, Marcia. “The Ethics of Clinical Research in the Third World.” *New England Journal of Medicine* 337.12 (1997): 847-9.

<sup>80</sup> “U.S. Public Health Service Syphilis Study at Tuskegee.” *Centers for Disease Control and Prevention*, US Department of Health & Human Services (30 Aug. 2017) [www.cdc.gov/tuskegee/timeline.htm](http://www.cdc.gov/tuskegee/timeline.htm).

<sup>81</sup> Freedman, et al., *op. cit.*

economies and employed placebo-treated control groups, “despite the fact that zidovudine has already been clearly shown to cut the rate of vertical transmission greatly and is now recommended in the US for all HIV-infected pregnant women.”<sup>82</sup> These examples can be seen as pointing not only at the fact that placebo-controlled trials may carry risks for the placebo-treated patients, but also at the fact that informed consent, protection of vulnerable subjects, and presence of specific risks connected with international trials should be taken into consideration.

Second, from the regulatory point of view, the rule of thumb applicable to placebo-controlled trials is included in the Declaration of Helsinki.<sup>83</sup> Article 33 of the Declaration of Helsinki reads:

“[t]he benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.”<sup>84</sup>

The Declaration has been object of extensive reforms in the past years, and many have discussed its role in the context of placebo-controlled clinical trials’ regulation.<sup>85</sup> In a nutshell, the rule foreseen in the Declaration prescribes that placebo-controlled trials should be conducted only when no “best proven intervention(s)” i.e. treatment exists, with two exceptions: (a) the presence of “compelling and scientifically sound methodological reasons” or (b) subjects assigned to the placebo treatment, would not be subject to “additional risks of serious or irreversible harm.”

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<sup>82</sup> Angell, *op. cit.*

<sup>83</sup> World Medical Association (WMA). *Declaration of Helsinki. Ethical principles for Medical Research Involving Human Subjects*. adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, last amended in October 2013.

<sup>84</sup> *Ibid.*

<sup>85</sup> See e.g. Lewis, John A., et al. “Placebo-Controlled Trials and the Declaration of Helsinki.” *The Lancet* 359.9314 (2002): 1337-1340. Carlson, Robert V. et al. “The Revision of the Declaration of Helsinki: Past, Present and Future.” *British Journal of Clinical Pharmacology* 57.6 (2004): 695-713. And Carpenter Jr., William T. et al., “The Declaration of Helsinki and Clinical Trials: a Focus on Placebo-Controlled Trials in Schizophrenia.” *American Journal of Psychiatry* 160.2 (2003): 356-362.

While the standard set by the Declaration has been considered the most relevant by many authors,<sup>86</sup> Lie et al. have developed an insightful comparative study, trying to assess the existence and content of an “international consensus opinion.”<sup>87</sup> According to the study, such consensus opinion would be based on three elements – valid science, social benefits, and favorable individual risk-benefit ratio – and could be seen as emerging from the positions taken over time by the Council for International Organization of Medical Sciences (CIOMS), the European Group on Ethics in Science and New Technologies (EGE), the National Bioethics Advisory Commission (NBAC), and the UN Program on HIV/AIDS (UNAIDS).<sup>88</sup> While adjudicating between the Declaration of Helsinki and the “international consensus opinion” as identified by Lie et al. goes beyond the scope of this contribution, the two standards are worth being taken into consideration. In fact, especially in the context of international clinical trials, a narrow interpretation of the Declaration of Helsinki would seem to exclude the legality of placebo-controlled trials when a *better* standard of care would otherwise be available (even in countries in which such standard of care would not be the regularly available one); on the contrary, the reliance on ethical standards different than the Declaration’s ones could allow for the legitimation of international trials conducted respecting *local* standards of care for placebo-patients.

Third, an increased vulnerability in placebo-controlled trials exists in the case of trials conducted in developing economies; in particular, due to the fact that in the case of those trials subjects may belong to communities that otherwise would have no access to any of the treatments available worldwide.<sup>89</sup> As noted by Angell, those who justify the conducting of clinical trials in developing countries e.g. on the vertical transmission of HIV, as described above, do so for two reasons: first, the placebo-patients in those areas would not receive treatment anyway so “investigators are simply observing what would happen to the subjects’ infants if there were no study;”<sup>90</sup> and second, a placebo-controlled study is the most efficient way to obtain results, from which also the patients’ community

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<sup>86</sup> Ibid.

<sup>87</sup> Lie, Reidar K., et al. “The Standard of Care Debate: the Declaration of Helsinki Versus the International Consensus Opinion.” *Journal of Medical Ethics* 30.2 (2004): 190-193.

<sup>88</sup> Ibid.

<sup>89</sup> Cf. Emanuel, Ezekiel J., et al. (2004), *op. cit.*

<sup>90</sup> Angell, *op. cit.*

will benefit.<sup>91</sup> Those who, instead, express concerns for placebo-controlled studies, do so relying on the standard set in the abovementioned Declaration of Helsinki: as the wording of the declaration clearly refers to the “best standard of care” test, substituting it with the best locally available standard of care would merely be an exercise of ethical relativism.<sup>92</sup>

Fourth, in clinical trials’ regulation and literature, several instruments and authors have attempted to clarify why and how the two positions described above should be balanced in practice. In general, they tend to depart from the acknowledgment that while placebo-controlled trials – especially when taking place in developing countries – remain controversial, there is no univocal way of labeling them as unethical or *per se* illegal. For example:

(a) Guideline n. 5 of the International Ethical Guidelines for Health-related Research Involving Humans advises host (developing) countries to take precautions in the context of international placebo-controlled trials.<sup>93</sup> The two pieces of advice consist of: seeking expert opinion “as to whether use of placebo may lead to results that are responsive to the needs or priorities of the host country” and “ascertain whether arrangements have been made for the transition to care after research for study participants (...), including post-trial arrangements for implementing any positive trial results, taking into consideration the regulatory and health care policy framework in the country.”<sup>94</sup>

(b) Some authors place emphasis on the efficacy of placebo-controlled trials and the concept of harm. According to those authors, valid scientific reasons support the use of placebo-controlled trials *vis-à-vis* active-control trials.<sup>95</sup> Furthermore, the rule of thumb to be applied when deciding whether placebo-controlled trials are appropriate depends on the risk of harm for the participating subjects. In this context, some conclude that placebo-controlled trials should be deemed acceptable when patients are not absolutely

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<sup>91</sup> Ibid.

<sup>92</sup> Ibid.

<sup>93</sup> Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), *International Ethical Guidelines for Health-related Research Involving Humans* (Geneva, 2016).

<sup>94</sup> International Ethical Guidelines for Health-related Research Involving Humans, op. cit., *Commentary to Guideline n. 5*.

<sup>95</sup> Temple, Robert, and Susan S. Ellenberg. “Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments. Part 1: Ethical and Scientific Issues.” *Annals of Internal Medicine* 133.6 (2000): 455-463.

harmed.<sup>96</sup> However, some suggest that best-available therapy control groups should not be preferred to placebo-groups as far as the risk of harm for participants is small and the trial “offers potential benefit to the subjects.”<sup>97</sup>

(c) Finally, other authors place emphasis on the need for balancing of different interest and the concept of favorable risk-benefit ratio. In this context, clinical trials that lack an immediate or obvious benefit for local populations should be addressed on a case-by-case basis.<sup>98</sup> Furthermore, in particular, the risk-benefit ratio should be assessed “by comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations.”<sup>99</sup>

To conclude, the right to health meets the technical and regulatory aspects of clinical trials in many connection points, including within the debate over ethical and legal standards to be applied to placebo-controlled trials. In this context, legislators should take into consideration at least three challenging aspects: the existence of *harm to subjects*, the *role of international guidelines and ethical standards* such as the Declaration of Helsinki, and the dichotomy between the “best standard” rule and the “*local standards*” option. As of their regulatory options, binding rules at the international level could be introduced to ensure that: a clear standard to assess when placebo-controlled trials should be deemed appropriate is established and corollary rules to guarantee the protection of the clinical trials subjects’ interest in their right to health.

### III. Right to Information

The second set of concerns related to the protection of human subjects in clinical trials belongs to the right to information discourse. Therefore, the following sections will provide the reader with, first, some introductory remarks concerning the right to information in the healthcare context, in general; and second, with some a discussion of

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<sup>96</sup> Temple, and Ellenberg, *op. cit.*

<sup>97</sup> Gupta, Usha and Menka Verma. “Placebo in Clinical Trials.” *Perspectives in Clinical Research* 4.1 (2013): 49-52.

<sup>98</sup> Weigmann, Katrin. “The Ethics of Global Clinical Trials.” *European Molecular Biology Organization Reports* 16 (2015): 566–70.

<sup>99</sup> Emanuel, Ezekiel J., et al. “What Makes Clinical Research Ethical?” *Journal of American Medical Association* 283.20 (2000): 2701-2711. And Emanuel et al. (2004), *op. cit.*

the most relevant issues connected with the right to information in the clinical trials context.

*(1) Right to Information: Introductory Notions*

In the context of healthcare law and policy, the right to information can be seen as touching upon two main issues: the rules to be applied to the information that concerns individuals and that is entered in the system (e.g. medical records) and the rules to be applied to the information that is transmitted by the system to the patient (e.g. informed consent). Furthermore, there is a general understanding within healthcare law and policy literature that regulatory decisions taken concerning the field of right to information entail an exercise in balancing two interests: the benefit in terms of public health, and the autonomy of the patient.<sup>100</sup> The balancing exercise becomes clear in practical terms when one – following Gostin et al. – puts, for example, at one end of the spectrum interests such as the social good of the collection of health data, and at the other end, the individual good of privacy protection.<sup>101</sup>

First, with regard to the treatment to be reserved to the information that regards individuals and is entered into the system, healthcare literature expresses two recurring concerns: one for data management regulations, and another for the scope of publicity of healthcare data.<sup>102</sup> In a nutshell, the first concern is related to the measures to be implemented in order for private patients' information to remain private, while the second concern is associated with the balancing of privacy interests with the general public interest in access to patients' information e.g. in the context of communicable diseases' control. Second, with regard to the rules to be applied to the information that is transmitted by the system to the patient, the main concern revolves around the nature and scope of the notion and the practical operation of informed consent.<sup>103</sup> Within the discussion of informed consent, following Faden and Beauchamp, it is not uncommon to

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<sup>100</sup> See e.g. Brown, Ian, and Andrew A. Adams. "The Ethical Challenges of Ubiquitous Healthcare." *International Review of Information Ethics* 8.12 (2007): 53-60.

<sup>101</sup> Gostin, Lawrence O., et al. "The Public Health Information Infrastructure: A National Review of the Law on Health Information Privacy." *Journal of American Medical Association* 275.24 (1996): 1921-1927.

<sup>102</sup> See e.g. Brown and Adams, *op. cit.*; and Gostin, et al., *op. cit.*

<sup>103</sup> See Faden, Ruth R., and Tom L. Beauchamp. *A History and Theory of Informed Consent* (Oxford University Press, 1986). Appelbaum, Paul S., et al. *Informed Consent: Legal Theory and Clinical Practice* (Oxford University Press, 1987). And Manson, Neil C., and Onora O'Neill. *Rethinking Informed Consent in Bioethics* (Cambridge University Press, 2007).

adopt either a pragmatic-legal approach – where the focus lies on the duty of the physician to ask for the patients’ consent and the consequent liability – or a philosophic-moral approach – where the focus is on the patients’ right to make autonomous choices.<sup>104</sup>

Both in the context of access to medical records and informed consent, many contributions have attempted to list and balance the interests involved. Interests that swing the balance towards an increased publicity of healthcare-related information touch upon patients’ autonomy and self-determination, as well as on the general public interest in health services research and public health.<sup>105</sup> Contributors that advocate for an increase in the access to information also claim that it is connected with an increased productivity on the part of healthcare providers, a low error rate, an increased quality of care, an increased level of trust in the doctor-patient relationship, increased positive competition among healthcare providers, and an improvement in terms of public participation in healthcare policy decisions.<sup>106</sup> On the other hand, some have noted how increasing the access to information in healthcare would result in adverse effects on the protection of privacy interests and an increment in costs (especially those related to compliance).<sup>107</sup> While presenting a possible interpretation of the balancing exercise between those interests and concerns in the general context of healthcare law and policy goes beyond the scope of this contribution, it is nevertheless important to take note of those elements, as they can also be found in the field of clinical trials.

## *(2) Right to Information in the Context of Clinical Trials*

The following paragraphs of this section will discuss how the interests of stakeholders in clinical trials interact in the context of two core regulatory issues related to the right to information in healthcare: the publicity of data and the nature and scope of informed consent. While the issue of publicity of data can be seen as intrinsically connected with the role, creation, and implementation of clinical trial registries (which will be addressed

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<sup>104</sup> Faden, and Beauchamp, *op cit.*, 4.

<sup>105</sup> Sage, William M. “Regulating Through Information: Disclosure Laws and American Health Care.” *Columbia Law Review* 99 (1999): 1701.

<sup>106</sup> Sage, *op. cit.* Jacob, J. “Consumer Access to Health Care Information: Its Effect on the Physician-Patient Relationship.” *Alaska Medicine* 44.4 (2002): 75-82. And Smolij, Kamila, and Kim Dun. “Patient Health Information Management: Searching for the Right Model.” *Perspectives in Health Information Management* vol. 3 (American Health Information Management Association, 2006).

<sup>107</sup> Sage, *op. cit.*

later in this thesis – within Chapter Six), the section dedicated to informed consent will address both the issue of the practical collection of the informed consent and that of organizing a fair and transparent recruitment process (and will be presented in the following paragraphs, within this chapter).

*(a) Clinical Trials Registries*

Clinical trials registries are databases of privately- and publicly-funded clinical studies conducted within single countries or worldwide. Understanding their rationale, history, and functioning is particularly interesting in the context of this thesis. Therefore, Chapter Six in this thesis is entirely dedicated to an analysis of clinical trials registries.

*(b) Informed Consent*

At the time of writing, the latest wave of debate over informed consent in clinical research is hitting the US, partially due to the new-found popularity of the story of Henrietta Lacks. A sample tissue taken from Ms. Lacks, a young black woman, in 1951 – was used to create the first immortal human cell line and, as of today, is still pervasively used in laboratories over the world.<sup>108</sup> The story of Henrietta Lacks raised several questions regarding the right of information in clinical research and several contributors have touched on it to address issues related to informed consent, commercialization and compensation, privacy and confidentiality, race, poverty, and health disparities, familial implications of genetic information, and trust in biomedical research.<sup>109</sup> Despite the fact that her contacts with clinical research did not directly concern clinical trials, the considerations applicable to it tend to be easily transferable to the context of clinical trials.

In the context of clinical trials regulation, informed consent is one of the pivotal elements that need to be addressed. Patients' participation in clinical trials should be informed and voluntary.<sup>110</sup> Therefore, for the purpose of this section, the issue will be divided into two

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<sup>108</sup> Zielinski, Sarah. "Henrietta Lacks' 'Immortal' Cells." *Smithsonian.com*, Smithsonian Institution, 22 Jan. 2010, [www.smithsonianmag.com/science-nature/henrietta-lacks-immortal-cells-6421299/](http://www.smithsonianmag.com/science-nature/henrietta-lacks-immortal-cells-6421299/).

<sup>109</sup> Beskow, Laura M. "Lessons from HeLa cells: the ethics and policy of biospecimens." *Annual review of genomics and human genetics* 17 (2016): 395-417.

<sup>110</sup> Lavori, Philip W., et al. *op. cit.* Flory, James, and Ezekiel Emanuel. "Interventions to Improve Research Participants' Understanding in Informed Consent for Research: A Systematic Review." *Journal of American Medical Association* 292.13 (2004): 1593-1601. Dunn, Laura B., and Dilip V. Jeste. "Enhancing Informed Consent for Research and Treatment." *Neuropsychopharmacology* 24.6 (2001):

sub-topics: first, the concerns that specifically touch upon the collection and understanding of the agreement that conveys participants' *informed* consent. Second, the concerns that apply to *voluntariness* (particularly in the phase of recruitment). They regard not only the tailoring of the sample and the underrepresentation of certain portions of the population but also – and more specifically – the issues emerging from the risk of coercion and the role of remuneration in clinical trials.

*(i) Informed Consent Per Se*

First, as noted by Beauchamp and Childress, informed consent in the context of clinical research can be seen as a process that encompasses five steps.<sup>111</sup> Lavori et al. summarized the steps as follows:

“1. Assessing the decision-making capacity or competence of the prospective research volunteer. 2. Disclosing relevant information about the proposed research. 3. Ensuring that the prospective volunteer understands the information. 4. Ensuring that the prospective volunteer be positioned to make a voluntary choice. 5. Authorizing a decision by the prospective volunteer and, if affirmative, having him or her sign a consent form.”<sup>112</sup>

In a nutshell, the goal of informed consent is to inform the patient about the treatment/procedure, to present benefits, risks, and alternative treatments/procedures with the intent of allowing him or her to make an autonomous decision.<sup>113</sup>

Second, reliance on those steps and the prevalence of the idea that informed consent represents both a right for patients and a duty for investigators is a modern phenomenon.<sup>114</sup> In the 1980s and 1990s, research conducted by Taylor et al. and Williams and Zwitter, highlighted both concerns expressed by physicians and the results of those concerns in practical terms (in European countries).<sup>115</sup> The main concerns of

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595-607. And Emanuel, Ezekiel J. *Ethical and regulatory aspects of clinical research: Readings and commentary* (Johns Hopkins University Press, 2003).

<sup>111</sup> Beauchamp, T.C., and J.F. Childress, *Principles of Biomedical Ethics*, 4th edition (Oxford University Press, 1994).

<sup>112</sup> Lavori, et al., *op. cit.*

<sup>113</sup> Ellis, P.M. “Attitudes towards and Participation in Randomised Clinical Trials in Oncology: A Review of the Literature.” *Annals of Oncology* 11.8 (2000): 939-945.

<sup>114</sup> Grady, Christine. “Enduring and Emerging Challenges of Informed Consent.” *New England Journal of Medicine* 372.9 (2015): 855-862.

<sup>115</sup> Taylor, Kathryn M., et al. “Physician Response to Informed Consent Regulations for Randomized Clinical Trials.” *Cancer* 60.6 (1987): 1415-1422. And Williams, C.J., and Matjaž Zwitter. “Informed

physicians related to their role – when they considered their definition of the medical profession as incompatible with the regulation of informed consent –, their autonomy – when they perceived informed consent as a loss of their own – and their relationship with patients.<sup>116</sup> The practical result of those concerns was a low rate of use of written consent, the use of information without authorization, a high rate of reliance on verbal consent only, and in cases in which the consent was sought and obtained, a tendency not to share all potentially relevant information.<sup>117</sup> Nowadays, a shift can be observed from the focus on the concerns expressed by physicians to the focus on patient protection.<sup>118</sup> Consistently, in many contexts, detailed informed consent procedures and information constitute integral tenets of the process of approval of clinical trials.<sup>119</sup> Nevertheless, it is worth noting that physicians’ concerns regarding the goal of advancing medical knowledge still exist,<sup>120</sup> that physicians still experience difficulties in conciliating their role of caring professional and that of experimenter,<sup>121</sup> and that there are *de facto* means for obtaining informed consent that discourage participation more than others.<sup>122</sup> Therefore, it is important to note that regulating informed consent entails an exercise in balancing the need to provide patients with information to preserve their autonomy and the need to balance physicians’ concerns that touch upon the possible effects of informed consent collection procedures on the recruitment rate.<sup>123</sup>

Third, there are recurring issues that affect the practical result of informed consent. Scholars consistently attempt to provide solutions to those issues, in order to allow legislators to better structure their informed consent regulation in clinical trials. Among the main issues often identified in literature, are the three discussed by Brown et al.: (i)

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Consent in European Multicentre Randomised Clinical Trials – Are Patients Really Informed?” *European Journal of Cancer* 30.7 (1994): 907-910.

<sup>116</sup> Taylor, et al., *op. cit.*

<sup>117</sup> Williams, and Zwitter, *op. cit.*

<sup>118</sup> Brown, R.F., et al. “Developing Ethical Strategies to Assist Oncologists in Seeking Informed Consent to Cancer Clinical Trials.” *Social science & medicine* 58.2 (2004a): 379-390.

<sup>119</sup> *Ibid.*

<sup>120</sup> *Ibid.*

<sup>121</sup> Brown, R.F., et al. “Seeking Informed Consent to Cancer Clinical Trials: Describing Current Practice.” *Social science & medicine* 58.12 (2004b): 2445-2457.

<sup>122</sup> Davis, Terry C., et al. “Informed Consent for Clinical Trials: A Comparative Study of Standard Versus Simplified Forms.” *Journal of the National Cancer Institute* 90.9 (1998): 668-674.

<sup>123</sup> Cf. Ellis, *op. cit.*

the risk of patients that do not understand the rationale for trials, (ii) the risk of patients poorly recalling the information obtained, and (iii) physiological and psychological impairing patients from making an informed decision.<sup>124</sup> Brown's findings are consistent with other contributions, such as that of Joffe et al., who found that while 90% of the participants in their study considered themselves well informed, 63% did actually not recognize the potential for incremental risk from participation and 70% did not recognize the unproven nature of the treatment.<sup>125</sup> Many studies have tested means to obtain informed consent in order to assess whether some increase the quality of patients' understanding – when possible, without decreasing the chances of recruitment. For example, despite the widespread idea that the use of multimedia and enhanced consent forms (e.g. condensing their length, revising content or form to make them more readable, adding graphics, etc.) may contribute to a better understanding on the side of patients, empirical research has established that they do not correspond to any improvement. Instead, it is useful to note that increased knowledge in patients is associated with: the introduction of a neutral educator to talk one-to-one to participants,<sup>126</sup> not signing the consent form at the initial discussion, the presence of a nurse, and the careful reading of the consent form.<sup>127</sup>

Fourth, in the case of international clinical trials, especially if conducted in developing economies, specific concerns arise in addition to those listed above. Concerns are connected, first, with the difference in the effectiveness of informed consent procedures between clinical trials that take place in developed and developing economies and, second, with the specific challenges that emerge for clinical trials conducted in developing economies.

With regard to the first category of concerns, for example, Marshall et al. observed the differences between pools of participants who took part in clinical trials respectively in the US and in Nigeria.<sup>128</sup> 99% of respondents in the US but only 72% of Nigerian

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<sup>124</sup> Brown, et al. (2004b) *op. cit.*

<sup>125</sup> Joffe, Steven, et al. "Quality of Informed Consent in Cancer Clinical Trials: A Cross-Sectional Survey." *The Lancet* 358.9295 (2001): 1772-1777.

<sup>126</sup> Flory and Emanuel, *op. cit.*

<sup>127</sup> Joffe, et al., *op. cit.*

<sup>128</sup> Marshall, Patricia A., et al. "Voluntary Participation and Informed Consent to International Genetic Research." *American Journal of Public Health* 96.11 (2006): 1989-1995.

respondents reported being told the study purpose. 97% of participants in the US reported that they could withdraw, compared with only 67% in Nigeria.<sup>129</sup>

With regard to the second category of concerns, Hyder and Wali, following their study on the practical approaches used by researchers in developing economies, found that 66% of them considered the informed consent process to be too focused on the individual rather than the family/community and in 35% of cases local staff shortened or simplified the informed consent procedure compared with the original protocol.<sup>130</sup> Interestingly, their study also showed that only 50% of researchers the participants in their clinical trials understood the concept of placebo and that only 84% of researchers participants were usually aware that they were in a research study.<sup>131</sup>

The goal, in those contexts, is not only that of obtaining truly informed consent but also of obtaining “culturally relevant” consent.<sup>132</sup> Bhutta compiled a useful list of “areas of disagreement” in which merely exporting standards and concerns arose in developed economies may not be in the best interest of clinical trials participants’ in other countries. In particular, those areas regard: (i) the focus on written consent which is traditionally used in developed economies but may not represent a guarantee of protection of participants’ interests in other areas of the world; (ii) the complex language used in written documentation, the length of consent forms, the alternative means to be used in case of illiterate populations; and (iii) the role of consent in traditional societies (communal, familiar, and/or individual).<sup>133</sup> Consistently, Marshall noted pointed out that “[s]ociocultural influences on comprehension of information, perceptions of risk, and beliefs regarding decisional authority” are to be considered when approaching the issue of informed consent in international clinical trials.<sup>134</sup>

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<sup>129</sup> Ibid.

<sup>130</sup> Hyder, Adnan A., and Salman A. Wali. “Informed Consent and Collaborative Research: Perspectives from the Developing World.” *Developing World Bioethics* 6.1 (2006): 33-40.

<sup>131</sup> Ibid.

<sup>132</sup> Mystakidou, Kyriaki, et al. “Ethical and Practical Challenges in Implementing Informed Consent in HIV/AIDS Clinical Trials in Developing or Resource-Limited Countries.” *SAHARA-J: Journal of Social Aspects of HIV/AIDS* 6.2 (2009): 46-57.

<sup>133</sup> Bhutta, Zulfiqar A. “Beyond Informed Consent.” *Bulletin of the World Health Organization* 82 (2004): 771-777.

<sup>134</sup> Marshall, Patricia A. “Informed Consent in International Health Research.” *Journal of Empirical Research on Human Research Ethics* 1.1 (2006): 25-41.

Stakeholders willing to express an opinion on the regulation of international clinical trials should take into consideration the concerns derived from these data. Possible strategies to address such issues entail using innovative materials and processes, using alternative processes for documentation, and involving senior staff and communication express in the obtainment of informed consent.<sup>135</sup> More specific suggestions regard the goal of tailoring informed consent to the sex and developmental age of participants as well as using local languages and involving community leaders and local cultural representatives in the process.<sup>136</sup>

*(ii) The Issue of Payment in the Recruitment Process*

Recruitment represents one of the pivotal moments in any clinical research study. In general terms, it can be defined as the “dialogue which takes place between an investigator and a potential participant prior to the initiation of the consent process.”<sup>137</sup> The recruitment-phase entails two goals: recruiting a sample that adequately represents the target population and recruiting a sufficient number of participants to meet the targeted sample size.<sup>138</sup> The main concerns that arise in connection with recruitment tend to focus on the role of payment of clinical trials subjects.<sup>139</sup> When assessing the ethical appropriateness, effectiveness, and legality of payment policies in clinical trials, practice varies significantly.

First, in general, investigators and sponsors are divided. Some see the use of payment in clinical trials as “wrong” and coercive *per se*, some see it as a potentially effective tool.<sup>140</sup> On the one hand, concerns often focus on the potential risk of coercion, undue inducement, a disproportionate burden on participants with financial problems, and

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<sup>135</sup> Bhutta, *op. cit.*

<sup>136</sup> Mystakidou, et al., *op. cit.*

<sup>137</sup> Patel, Maxine X., et al. “Challenges in Recruitment of Research Participants.” *Advances in Psychiatric Treatment* 9.3 (2003): 229-238.

<sup>138</sup> Ibid.

<sup>139</sup> See Grady, Christine. “Payment of Clinical Research Subjects.” *Journal of Clinical Investigation* 115.7 (2005): 1681. Emanuel, et al. (2004), *op. cit.* Hulley, Stephen B., et al. *Designing Clinical Research* (Lippincott Williams & Wilkins, 2013). And Dickert, Neal, and Christine Grady. “What’s the Price of a Research Subject? Approaches to Payment for Research Participation.” *New England Journal of Medicine* 341 (1999): 198-203.

<sup>140</sup> Grady (2005), *op. cit.*

commodification.<sup>141</sup> The challenge with assessing such risks is often dependent upon subjective factors. On the other hand, supporters of the use of payment highlight the value that it may have in encouraging participation and promoting the goal of achieving ethnic and gender diversity within the sample of participants.<sup>142</sup> They also see payment as “an indication of respect for the time and contribution that research subjects make.”<sup>143</sup> The complexity of the issue increases in the case of clinical trials involving children, where the need to obtain consent from parents and the challenge of structuring payment as a “token gesture of appreciation” represent pervasive concerns.<sup>144</sup>

Second, in practical terms, it is unclear how common the practice of economically rewarding participants is. Grady noted that there is some variation depending on medical subspecialties.<sup>145</sup> Furthermore, data are hard to collect, given that few organizations have written policies on payment and review boards often decide with little specific guidance.<sup>146</sup> Practice also varies, as to how investigators and sponsors decide to present payment to research subjects: in some cases payment serves as an incentive, in some as compensation (i.e. wage-payment), in some as reimbursement and in some as a sign of appreciation (i.e. “mere” reward).<sup>147</sup>

Third, while there seems to be no clear-cut ethical rule allowing or prohibiting reliance on payments in order to incentivize recruitment, it may be relevant to list some of the potential strategies implementable to avoid the risk of coercion and undue inducement. Concerns may be addressed by (i) carefully tailoring eligibility criteria,<sup>148</sup> (ii) establishing mechanisms to calculate payments on the basis of criteria e.g. the level of risk entailed in the study,<sup>149</sup> and also (iii) addressing via full disclosure the potential

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<sup>141</sup> Ibid.

<sup>142</sup> Ibid.

<sup>143</sup> Grady, Christine. “Money for Research Participation: Does It Jeopardize Informed Consent?” *American Journal of Bioethics* 1.2 (2001): 40-44.

<sup>144</sup> Tishler, Carl L., and Natalie Staats Reiss. “Pediatric Drug-Trial Recruitment: Enticement Without Coercion.” *Pediatrics* 127.5 (2011): 949-954.

<sup>145</sup> Grady (2005), *op. cit.*

<sup>146</sup> Dickert, Neal, et al. “Paying Research Subjects: An Analysis of Current Policies.” *Annals of Internal Medicine* 136.5 (2002): 368-373.

<sup>147</sup> Grady (2005), *op. cit.*

<sup>148</sup> Ibid.

<sup>149</sup> Tishler, and Staats Reiss, *op. cit.*

conflicts of interest posed not only by the remuneration of participants but by the remuneration of medical personnel for patient recruitment.<sup>150</sup>

To conclude, relevant concerns exist and apply both during the recruitment-phase and at the moment of the collection of informed consent. Being aware of such issues and of the different interests involved in their solution is important for any legislator wishing to structure a clinical trials regulation.

#### IV. Preliminary Conclusions

To conclude, with regard to the right to information – whether seen as an autonomous right in the healthcare context or as sub-stratum of the general right to health –, it can be noted that it represents a relevant lens through which the regulation of clinical trials can be observed and promoted. In the specific context of clinical trials, risk and opportunities related to the right of information can be analyzed studying the evolution of clinical trials registries as well as the issue of informed consent. In both contexts, different stakeholders have sometimes aligned and sometimes competing interests. Nevertheless, legislators can rely on a wide range of inputs produced by different stakeholders, both to identify issues to be regulated and ways in which effectively address them.

At the same time, while the status of the definition, scope, and binding nature of the right to health in international law remain controversial, its role in the framework of clinical trials regulation raises several practical issues. In particular, relevant challenges emerge in the context of sampling and tailoring goals and techniques as well as in the context of placebo trials and standards of care. While prospective legislators should not underestimate those issues, either at the national or international level, they confirm to a certain extent the need for a global perspective on clinical trials regulation. In fact, while some challenges to the right to health in the context of clinical trials can be effectively regulated at the national level e.g. the issue of sample sizing, other depend on the international dimension of contemporary clinical trials e.g. the relevance of standards of care in placebo-controlled trials and can therefore be better addressed at the international level.

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<sup>150</sup> Brown, et al. (2004b) *op. cit.*

## **CHAPTER THREE: COMPETING PARADIGMS IN CLINICAL TRIALS POLICY AND REGULATION**

### *I. Introduction*

As noted by Gostin et al., studying the law and the health system requires acknowledging that three pulling and pushing forces need to be balanced: the pursuit of access, cost, and quality.<sup>151</sup> They can be seen as competing paradigms and as shadows under which the – often competing – interests of the stakeholders involved in clinical trials meet. Instead, their definition will tend to vary on the basis of the stakeholder entrusted with the role of defining them.

With regard to the three competing paradigms, in the general context of healthcare regulation, it can be noted that the paradigm of access concerns both the access of healthcare users (patients) to treatment and the access of healthcare providers (primarily physicians but – in privatized healthcare systems – also intermediaries such as insurances) to the healthcare market; the paradigm of quality chiefly concerns the level of quality of the care provided; and the paradigm of costs mainly concerns the quality and quantity of healthcare costs – where “quality” pertains to the choice of level of public intervention in healthcare expenditure and “quantity” pertains the sheer economic cost of treatments. Tradeoffs between those concepts are inevitable when attempting to regulate healthcare systems.<sup>152</sup> In fact, regulatory interventions affecting any of those paradigms will likely produce results on one or more of the others. For example, expanding the pool of subjects with access to free healthcare will increase the pressure on the societal cost of healthcare.<sup>153</sup>

In the context of clinical trials, as will be shown later in this contribution, access, cost, and quality cannot be univocally defined, but one of the aims of this contribution is to provide for an application of such paradigms to the study of clinical trials regulation. Given that the three paradigms are no more than a means of reading the interests and

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<sup>151</sup> Lawrence O. Gostin, et al., *Law and the Health System* (University Casebook Series, Foundation Press, 2014)

<sup>152</sup> *Ibid.*, 57.

<sup>153</sup> *Ibid.*

concerns of the stakeholders involved in clinical trials, each section of this chapter will provide the reader with an analysis of the three paradigms specifically focused on the characteristics that they assume in the face of those interests and concerns. This activity will shed some light on what those paradigms mean for the different stakeholders involved in clinical trials regulation.

As for the relevant stakeholders, within clinical trials literature, there is no uniform identification of their definition and identity. However, broad interpretations of the concept encompass the following categories among the stakeholders: participants in clinical trials, funders and sponsors of trials, regulatory agencies, investigators, research institutions and universities, journals, and professional societies.<sup>154</sup> On the one hand, this contribution departs from such a broad categorization of clinical trials' stakeholders and narrows its perspective, focusing on three of them. The focus on three stakeholders is a result of two considerations: first, journals, investigators, research institutions, and professional societies can all be seen as falling within a broadened definition of investigators – a definition that focuses on seeing all of them as members of the scientific community. Second, in our opinion, encompassing regulatory agencies among the stakeholders risks portraying them as one of the parties interested in the regulation of clinical trials. On the contrary, regulatory agencies, as well as any institutional player, should not be seen as one of the weights in the balancing activity but as the weight scale entrusted with the role of conducting such balancing activity. On the other hand, this contribution marginally expands the definition of human subjects, pairing the focus on participants in clinical trials with that on patients. The latter category encompasses both the pool of subjects potentially interested in becoming participants in clinical trials and those who will potentially consume the products that obtained approval for use and commercialization following successful clinical trials.

Therefore, the next paragraphs will focus on human subjects, sponsors, and investigators as stakeholders. In this context, as noted above, human subjects encompass clinical trials participants, perspective participants, and consumers of post-clinical trials marketed products. Sponsors encompass all the subjects that are involved in commissioning and

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<sup>154</sup> Committee on Strategies for Responsible Sharing of Clinical Trial Data; Board on Health Sciences Policy; Institute of Medicine. *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk*. Washington (DC): National Academies Press (US); 2015 Apr. 20, The Roles and Responsibilities of Stakeholders in the Sharing of Clinical Trial Data. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK286000/>

funding clinical trials, both when they belong to the pharmaceutical industry and when they constitute public and nonprofit organizations. Investigators primarily encompass the clinicians involved in any stage of clinical trials; subjects that belong to this category are both the designers of clinical trials, the infrastructures (study-sites) and the professionals involved in the administration of the protocol created for the clinical trial (e.g. the physicians and nurses that will follow participants during the clinical trial), the secondary users that rely on clinical trial data for purposes different than the original one, the professional organizations that represent those professionals, and the scientific journals that publish the results of clinical trials.

To conclude, this chapter aims at describing what the paradigms of quality, cost, and access represent in the context of clinical trials regulation. For the purpose of this chapter, human subjects, sponsors, and investigators, will be considered as the relevant stakeholders.

## II. The Paradigm of Access

Within the paradigm of access, different stakeholders manifest different – sometimes competing – interests.

First, the interest in access for human subjects is a double-folded one.

On the one hand, the patients interested in taking part in clinical trials have an interest in open and transparent recruitment practices.<sup>155</sup> In general terms, this translates as an interest in recruitment standards that impose a prospective rigid identification of the recruitment criteria.<sup>156</sup> In more specific terms, for example, patients that belong to a population that has traditionally been more challenging to recruit and underrepresented in clinical trials have an interest in policies implemented to increase their access to clinical trials.<sup>157</sup> Those policies in principle would be capable of inducing positive results

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<sup>155</sup> Gelinas, Luke, et al. “When Clinical Trials Compete: Prioritising Study Recruitment.” *Journal Of Medical Ethics* (2017): medethics-2016.

<sup>156</sup> Lovato, Laura C., et al. “Recruitment for Controlled Clinical Trials: Literature Summary And Annotated Bibliography.” *Controlled Clinical Trials* 18.4 (1997): 328-352. And Hunninghake, Donald B., et al. “Recruitment Experience in Clinical Trials: Literature Summary and Annotated Bibliography.” *Controlled Clinical Trials* 8.4 (1987): 6-30.

<sup>157</sup> Ford, Jean G., et al. “Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review.” *Cancer* 112.2 (2008): 228-242. And Murthy, Vivek H., et al. “Participation in cancer clinical trials: race, sex-, and age-based disparities.” *Journal of the American Medical Association* 291.22 (2004): 2720-2726.

at the level of the quality of outcome of the clinical trials. Therefore, they represent an interest in which increased access (in qualitative terms) may translate into increased quality of the output. However, this reaction would also entail higher costs, given that measures to increase the recruitment of traditionally underrepresented populations would require higher investments in pre-recruitment advertisement and in compensation to participants.

On the other hand, participants in clinical trials – both prospectively and retrospectively – as well as the general public (prospective consumers) have an interest in access to information and data pertaining to clinical trials. The interest in the availability of such information has a value both in the context of the informed decision that prospective clinical trial participants must take before enrolling in a trial and in the context of the informed decision that prospective consumers can take.<sup>158</sup> On this issue, a partial alignment can be observed between the participants’ interest and the investigators’ interest, to the extent that transparency in clinical trials registration can be seen as a tool to reward participants’ trust and altruism and guarantee that communities will repeatedly commit to voluntarily participate in clinical research.<sup>159</sup> However, the possibility of misalignment exists in situations in which clinicians have observed the risk of a decreased enrollment rate proportional to the increase in the amount of information provided to prospective participants.<sup>160</sup> Also, among pulling factors in the context to access to information, the concerns of sponsors for the costs of divulging potentially valuable data can be observed, together with the interest of participants in the protection of personal and private sensitive data.<sup>161</sup>

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<sup>158</sup> Flory and Emanuel, *op. cit.*

<sup>159</sup> Sim, Ida, et al. “Clinical Trial Registration: Transparency is the Watchword.” *The Lancet* 367.9523 (2006): 1631-1633. And De Angelis, Catherine, et al. “Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors.” (2004): 1250-1251.

<sup>160</sup> Jenkins, V., and L. Fallowfield. “Reasons for Accepting or Declining to Participate in Randomized Clinical Trials for Cancer Therapy.” *British Journal of Cancer* 82.11 (2000): 1783. And Davis, Terry C., et al., *op. cit.*

<sup>161</sup> The Pharma Letter. “Concern Over US FDA Disclosure Plans.” *TPL*, [www.thepharmaletter.com/article/concern-over-us-fda-disclosure-plans](http://www.thepharmaletter.com/article/concern-over-us-fda-disclosure-plans). Wechsler, Jill. “The Push for Transparency: Risks, Costs, and Concerns.” *Pharmaceutical Executive Home*, 22 Dec. 2016, [www.pharmexec.com/push-transparency-risks-costs-and-concerns](http://www.pharmexec.com/push-transparency-risks-costs-and-concerns). And “Foundation Text.” *Current Issues in Research Ethics: Privacy and Confidentiality*, [ccnmtl.columbia.edu/projects/cire/pac/foundation/](http://ccnmtl.columbia.edu/projects/cire/pac/foundation/).

Second, the interest of investigators in access has two concrete contexts of application. The first is the access to information and data mentioned above. The first regulatory battle fought in this field has been one for mandatory trial registration. Within it, the interests of the general public and of scientific investigators have traditionally been aligned, to the point that it is following a decision of the International Committee of Medical Journal Editors (which mandated prospective registration of the clinical trials aiming at being published) that registration rates have steeply increased.<sup>162</sup> Access to information, from the perspective of investigators, has both the advantage of fostering a better relationship with prospective participants in the trial and the advantage of preventing the risks associated with selective publication.<sup>163</sup> It also increases the potential for the conduction of secondary investigations, based on meta-data obtained by the primary ones.<sup>164</sup>

The second category of access-related concerns for investigators regards the access to sponsors and to the system of credentials, when one is in place.<sup>165</sup> In many legal systems, access to the role of investigators is limited by the rate at which funding is available (both in the public system and in the private market), as well as by barriers to entry to the investigators' "market", e.g. minimum training requirements, accreditation infrastructures, etc. Such barriers, as with any traditional compliance tool, are correlated with a general interest in guaranteeing a good quality of clinical trials, but have an effect on their cost. Therefore, in this context, the investigators' concerns are often aligned with those of the sponsors.

Third, as stated above, sponsors share some of the investigators' concerns with regard to barriers to access and compliance.

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<sup>162</sup> Laine, Christine, et al. "Clinical Trial Registration—Looking Back and Moving Ahead." (2007): 2734-2736, published at [www.nejm.org](http://www.nejm.org) on June 4, 2007.

<sup>163</sup> Dickersin, Kay, and Drummond Rennie. "Registering Clinical Trials." *Journal of the American Medical Association* 290.4 (2003): 516-523. And De Angelis, Catherine, et al. *op. cit.*

<sup>164</sup> DerSimonian, Rebecca, and Nan Laird. "Meta-analysis in Clinical Trials." *Controlled Clinical Trials* 7.3 (1986): 177-188. Jadad, Alejandro R., et al. "Assessing the Quality of Reports Of Randomized Clinical Trials: Is Blinding Necessary?" *Controlled Clinical Trials* 17.1 (1996): 1-12. And Egger, Matthias, et al. "Bias in Meta-analysis Detected by a Simple, Graphical Test." *British Medical Journal* 315.7109 (1997): 629-634.

<sup>165</sup> See Followill, David S., et al. "Credentialing for Participation in Clinical Trials." *Frontiers in Oncology* 2 (2012). And, for example, "NCI Registration and Credential Repository (RCR)." *Cancer Therapy Evaluation Program (CTEP)*, [ctep.cancer.gov/investigatorresources/](http://ctep.cancer.gov/investigatorresources/).

At the same time, certain concerns are unique to the sponsors. This is the case for disclosure-related concerns that apply to information and data-sharing policies. In that context, sponsors – specifically, pharmaceutical companies that promote and organize clinical trials – tend to be reluctant to support and implement measures that will incentivize the disclosure of information garnered via clinical trials. Their position seems to emerge from the combination of three sub-concerns. The first relates to the protection of trade secrets – to the extent that information pertaining to their clinical trials is produced at a cost, and its divulgation may result in other sponsors taking advantage of it;<sup>166</sup> the second is related to any liability derived from breaches of the participants’ right to privacy;<sup>167</sup> while the third relates to the potential negative effects on the company’s reputation from any publicity regarding clinical trials that produce negative results.<sup>168</sup> Intuitively, a reduction in efforts to expand access e.g. to information garnered from clinical trials would lower the economic burden of compliance on sponsors and therefore result in lower costs, but this could negatively affect both the interests of investigators and human subjects to access as well as the paradigm of quality (to the extent that transparency is considered to produce positive effects on the quality, especially with regard to the safety of the results).

To conclude, the paradigm of access is a relevant one in clinical trials regulation and policy, and can assume different shapes, depending on the stakeholder in question. In some cases, stakeholders have aligned interests and concerns, while in others, their positions diverge. Nevertheless, policies that aim at expanding or restricting the influence of the paradigm of access or clinical trials regulations will produce results – be they negative or positive – on the competing paradigms of cost and quality.

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<sup>166</sup> Committee on Strategies for Responsible Sharing of Clinical Trial Data. “Legal Discussion of Risks to Industry Sponsors.” *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk.*, US National Library of Medicine, 20 Apr. 2015, [www.ncbi.nlm.nih.gov/books/NBK286001/](http://www.ncbi.nlm.nih.gov/books/NBK286001/).

<sup>167</sup> “Breach of Privacy Risks for Clinical Research Sponsors, Contributed by Jill E. Anderson, Moses & Singer LLP.” *Bloomberg BNA* (2011) [www.bna.com/privacy-risks-for-clinical-research-sponsors/](http://www.bna.com/privacy-risks-for-clinical-research-sponsors/). And Wadlund, Jill. “Heading Off a Clinical Trial Liability Lawsuit.” *Applied Clinical Trials Home*, 15 Nov. 2014, [www.appliedclinicaltrials.com/heading-clinical-trial-liability-lawsuit](http://www.appliedclinicaltrials.com/heading-clinical-trial-liability-lawsuit).

<sup>168</sup> Cf. Hunninghake, Donald B., et al. “Recruitment Experience in Clinical Trials: Literature Summary and Annotated Bibliography.” *Controlled clinical trials* 8.4 (1987): 6-30. And Stone, Judy. “How Can We Encourage Participation in Clinical Trials?” *Forbes*, Forbes Magazine, 8 Jan. 2015,

[www.forbes.com/sites/judystone/2015/01/06/how-can-we-encourage-participation-in-clinical-trials/#ac12c64d0c59](http://www.forbes.com/sites/judystone/2015/01/06/how-can-we-encourage-participation-in-clinical-trials/#ac12c64d0c59).

### III. The Paradigm of Cost

Similarly to what was observed above with regard to the paradigm of access, the paradigm of cost can be seen as a field of interaction of the three stakeholders' interests and concerns.

The paradigm of cost, for human subjects interested in clinical trials, encompasses two categories of costs. First, the cost of participation for patients involved in clinical trials.<sup>169</sup> This cost can be seen as the combination of direct and indirect expenses. Although some legal systems prevent sponsors from transferring these costs onto participants in clinical trials, direct expenses relate to the products that participants purchase in order to participate in clinical trials e.g. auxiliary medicinal products and medical devices used for the administration of the primary treatment. Indirect expenses may relate both to material indirect costs – e.g. travel expenses to reach the clinical trials site – and psychological costs, connected with the fact that taking part in trials is often an action dictated by trust in and altruism towards scientific progress. Often, sponsors implement financial mechanisms to reward participants for taking part in clinical trials;<sup>170</sup> this can be seen as an example of how, within the same paradigm, namely the paradigm of cost, the burden can actually be transferred from one subject to another.

The second cost of clinical trials falls on the general public, i.e. taxpayers. This cost can be seen as a function of both the public investment in medical research and development spent in publicly funded clinical trials and in the public investment in compliance measures such as inspections and auditing involving sponsors and investigators.<sup>171</sup>

In the case of investigators, the paradigm of cost has mainly to do with the costs of compliance e.g. with accreditation and credentialing procedures. As noted above, restrictions to access to the cadre of investigators are dictated by quality- and safety-related concerns, but result in an increase in terms of costs. Sponsors share similar

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<sup>169</sup> Martin, Paul J., et al. "Responsibility for Costs Associated With Clinical Trials." *Journal of Clinical Oncology* 32.30 (2014): 3357-3359. And, for example, "Paying for Clinical Trials." *National Cancer Institute*, [www.cancer.gov/about-cancer/treatment/clinical-trials/paying](http://www.cancer.gov/about-cancer/treatment/clinical-trials/paying).

<sup>170</sup> Spilker, Bert. "Methods of Assessing And Improving Patient Compliance in Clinical Trials." *IRB: Ethics & Human Research* 14.3 (1992): 1-6. And Grady, Christine (2005), *op. cit.*

<sup>171</sup> OECD (2001), *Measuring Expenditure on Health-related R&D*, OECD Publishing, Paris.

<http://dx.doi.org/10.1787/9789264192928-en>

concerns, as they are often responsible for the compliance of the investigators that they hire with clinical trials regulation.<sup>172</sup>

In the case of sponsors, in addition to the costs of compliance that simultaneously affect sponsors and investigators, the former often have to deal with the direct organizational and material costs of clinical trials.<sup>173</sup> These costs can be seen as a combination of the costs related to the materials necessary for the clinical trial (the treatment studied in the trial, auxiliary treatments, and administering tools), the costs for the recruitment of participants in clinical trials, and the costs for the investigation-personnel (medical and administrative) and facilities.

In sum, the paradigm of cost remains a relevant one in the context of clinical trials, and is connected with the actions and preferences of all three stakeholders. Actions taken to affect the paradigm of cost will often produce effects on the other two competing paradigms.

#### IV. The Paradigm of Quality

Finally, clinical trial dynamics often deal with the paradigm of quality. As in the case of the other paradigms, quality can have different meanings and focuses depending on the interested stakeholder.

Human subjects have a specific interest in two aspects of quality. First, the quality of clinical trials in terms of safety of the process that they entail. Prospective participants and patients who take part in clinical trials value rights that, when expanded, have an effect on the paradigm of quality. Amongst those rights, the right to informed consent, that to withdrawal from clinical trials, and the right to post-trial treatment may be identified.<sup>174</sup> Informed consent mainly relates to the need for patients to make an

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<sup>172</sup> Schulman, Kevin A., et al. "A National Survey of Provisions in Clinical-Trial Agreements Between Medical Schools and Industry Sponsors." *New England Journal of Medicine* 347.17 (2002): 1335-1341. And Prayle, Andrew P., et al. "Compliance with Mandatory Reporting of Clinical Trial Results on clinicaltrials.gov: Cross Sectional Study." *British Medical Journal* 344 (2012).

<sup>173</sup> Lexchin, Joel, et al. "Pharmaceutical Industry Sponsorship and Research Outcome And Quality: Systematic Review." *British Medical Journal* 326.7400 (2003): 1167-1170. And Emanuel, Ezekiel J., et al. "The Costs of Conducting Clinical Research." *Journal of Clinical Oncology* 21.22 (2003): 4145-4150.

<sup>174</sup> Cf. respectively, Edwards, Sarah JL, et al. "Informed Consent for Clinical Trials: in Search of the 'Best' Method." *Social science & medicine* 47.11 (1998): 1825-1840. Gul, Raisa B., and Parveen A. Ali. "Clinical Trials: The Challenge of Recruitment and Retention of Participants." *Journal of Clinical*

informed decision at the recruitment stage. While participants have an interest in this value, investigators and sponsors often advocate for simplified procedures because complex informed consent procedures have effects on the cost of recruitment and on the access – in terms of enrollment rate – to participants.

Second, the paradigm of quality intersects with the interests of human subjects in terms of the outcome of the process, namely, with regard to the quality of the treatment that is approved for administration and commercialization following the positive conclusion of a clinical trial.<sup>175</sup> In principle, clinical trials conducted in compliance with the highest quality standards of design and administration produce better results, and better results can contribute to the commercialization of more effective products. However, increases in terms of quality may be correlated with increased compliance cost and may eventually result in less clinical trials being conducted therefore causing reduced access to the latter or reduced outputs in terms of commercialized products.

Investigators share with human subjects the common interest in the quality of the output of clinical trials.<sup>176</sup> For the scientific community, in particular, the results of high-quality trials, i.e. those that are derived through scrupulous scientific methodologies and absent any procedural biases and data falsification, represent a stronger contribution to the advancement of scientific innovation. Even trials with negative results, in this sense, have the potential to positively influence further research.<sup>177</sup> Related the general goal of producing and receiving results of a high quality, are certain sub-interests of investigators, such as an interest in the quality of the materials and facilities to which they have access. as well as an interest in the quality of the pool of prospective

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*Nursing* 19.1-2 (2010): 227-233. And Doval, Dinesh Chandra, et al. “Post-Trial Access to Treatment for Patients Participating in Clinical Trials.” *Perspectives in Clinical Research* 6.2 (2015): 82.

<sup>175</sup> Cf. Talbot, George H. “Efficacy as an Important Facet of ‘Safety’ In Clinical Trials: How Can We Do Our Best For Our Patients?” *Clinical Infectious Diseases* 47 Supplement 3 (2008): S180-S185. And, for example, “Clinical Efficacy and Safety Guidelines.” *European Medicines Agency - Scientific guidelines - Clinical efficacy and safety guidelines*,

[www.ema.europa.eu/ema/index.jsp?curl=pages%2Fregulation%2Fgeneral%2Fgeneral\\_content\\_000085.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fregulation%2Fgeneral%2Fgeneral_content_000085.jsp)

<sup>176</sup> Tunis, Sean R., et al. “Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy.” *Journal of the American Medical Association* 290.12 (2003): 1624-1632.

<sup>177</sup> Cf. Spilker, Bert. “Quality of Life and Pharmacoeconomics in Clinical Trials.” (1995). And Jüni, Peter, et al. “Systematic Reviews in Health Care: Assessing the Quality of Controlled Clinical Trials.” *British Medical Journal* 323.7303 (2001): 42.

participants to which they have access (in terms of correspondence with the ideal subjects on which the treatment ought to be tested).

Finally, sponsors can be seen as having their main quality-related interest in the quality of the *outcome* of the clinical trials. Considering that the sponsor is often the subject that has a direct interest in the profits deriving from the approval of any tested treatment – be they “social” profits when the clinical trial is publicly funded or sheer financial profits when the treatment tested is approved for commercialization on the market. The case for absolute quality – and thus, safety – of the outcome of clinical trials is a strong one as, in principle, any stakeholder and legislator share an interest in introducing only safe and effective products to the market.

To conclude, the paradigm of quality is pivotal in the context of clinical trials. However, in this context, it is important to observe that even the promotion of absolute values is influenced by competing paradigms and triggers different dynamics of which legislators should be aware. For example, in any system that decides to exclusively and absolutely focus on the paradigm of quality (namely, on the quality of the products commercialized following successful clinical trials), the effects of the cost paradigm will materialize, making it more expensive for investigators and sponsors to conduct clinical trials; this may result in investors pulling out of the clinical trials market or, in any event, on fewer clinical trials being promoted and conducted.

#### *V. The Three Paradigms and Clinical Trials gone Global*

The considerations presented thus far in this contribution aim at providing prospective reformers and legislators with some insights on the dynamics of clinical trials regulation. They stand independently from which institutional standpoint they are observed – being it that of a national legislator or an international organization. Nevertheless, it is worth noting that the existence of the three pulling-and-pushing paradigms and the interaction of the three relevant stakeholders may also be used to better understand clinical trials dynamics – and especially – in a moment in which clinical trials have become a global phenomenon.

The past decades have been characterized by a globalization of clinical trials.<sup>178</sup> The latter is the result of the “increased geographic dispersion of drug development operations.” In practical terms, it results in sponsors – more often than not based in developed economies – commissioning clinical trials in centers based in developing economies.<sup>179</sup> Although the phenomenon should not be confused with the tendency to conduct multi-centered clinical trials, global trials often involve research centers based in more than one country.<sup>180</sup> This trend has pushed both legislators and commentators to act and participate in the dialogue over the risks and opportunities of global clinical trials. Legislators have focused on regulatory challenges, such as those related to overseas inspections and credentialing;<sup>181</sup> commentators often analyze the scientific and ethical issues that can be raised when observing the globalization of clinical trials.<sup>182</sup>

In this context, this contribution does not aim at identifying the risks and opportunities connected with the globalization of clinical trials, or at suggesting possible solutions to the main regulatory challenges that they pose. Instead, it encompasses among its purposes that of suggesting how the three-paradigm model can also be applied in the context of global clinical trials.

The first way in which the model becomes relevant is *explanation*. This, in the context of global clinical trials, concerns more specifically the action of national and macro-regional policymakers and legislators. In particular, the tendency of clinical trials to go global may be seen as a “relief valve” for situations in which the three paradigms are out of balance and excessive pressure is exercised on one of them. For example, two of the main pushing forces that move sponsors to run clinical trials in developing economies are the difficulty in recruiting patients in developed economies and general economic advantages (in terms of the sheer cost of clinical care and operational compliance-related

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<sup>178</sup> Thiers, Fabio A., et al. “Trends in the globalization of clinical trials.” *Nature Reviews Drug Discovery* 7.1 (2008): 13-14. And Petryna, Adriana. *When experiments travel: clinical trials and the global search for human subjects* (Princeton University Press, 2009).

<sup>179</sup> Thiers, et al. *op. cit.*

<sup>180</sup> *Ibid.*

<sup>181</sup> E.g. Ayalew, Kassa, Office of Compliance Center for Drug Evaluation and Research Food and Drug Administration, *FDA Perspective on International Clinical Trials*, presentation available at <https://www.fda.gov/downloads/drugs/newsevents/ucm441250.pdf>

<sup>182</sup> E.g. Glickman, Seth W., et al. “Ethical and Scientific Implications of the Globalization of Clinical Research.” (2009): 816-823. Benatar, Solomon R., and Peter A. Singer. “A new look at international research ethics.” *British Medical Journal* 321.7264 (2000): 824. And Angell, *op. cit.*

costs).<sup>183</sup> The first factor can be seen as a function of the interest of investigators in data garnered from clinical trials; the second can be seen as a function of the interest of sponsors in cost-reduction. In a global context in which running clinical trials in developed economies represents an available option, understanding that when stakeholders perceive excessive pressure placed on one of the paradigms, they may choose to outsource clinical trials abroad, is an important notion for legislators based in developed economies.

The second way in which the three paradigms can be used in the context of global clinical trials is *application*. In fact, the three paradigms exist and represent pulling and pushing forces, also in the dynamic of global clinical trials. Understanding them – and the fact that they also exist at the global level – may serve international organizations interested in clinical trials regulation to better plan and structure their action. In this sense, the existence of the three competing paradigms and the shape that they take in the globalized industry of clinical trials is something of which international institutional actors should be aware.

VI. Preliminary Conclusions

To conclude, the paradigms of access, cost, and quality identified by Gostin et. al represent a useful tool to understand the background of clinical trials policy and legislation.

Table 1 provides an overview of the main interests and concerns that are relevant in this context.

Table 1			
Competing Paradigms in clinical Trials Policy and Regulation			
	Access	Cost	Quality
Human Subjects	(1) Access of participants to clinical trials	(1) Cost of participation	(1) Safety of clinical trials

<sup>183</sup> Ayalew, *op. cit.*

	(2) Public access to clinical trials data	(2) Cost of compliance	(2) Safety and effectiveness of the clinical trials' outcome
Investigators	(1) To sponsors and to credentialing systems (when existing)	(1) Costs of compliance	(1) Of clinical trials data
	(2) To clinical trials data		(2) Safety and effectiveness of the clinical trials' outcome
Sponsors	(1) To sponsors and to credentialing systems (when existing)	(1) Costs of clinical trials <i>per se</i>	(1) Of clinical trials data
	(2) Disclosure-related concerns	(2) Costs of compliance	(2) Safety and effectiveness of the clinical trials' outcome

Understanding how pulling and pushing on each of those competing paradigms will produce effects on the other two paradigms is an essential exercise that legislators should use, in order to better predict the results of clinical trials regulations and reforms. Furthermore, analyzing the way in which each stakeholder – human subjects, investigators, and sponsors – develops specific concerns and interests within each paradigm provides us with a better understanding of the dynamics of clinical trials, both at local and at international-global levels. Finally, the three paradigms can be used not only to better appreciate global clinical trials dynamics but also to better understand how the development of a global dimension of clinical trials represents a “relief valve” when the three paradigms are unbalanced at the local level.

This chapter aimed at providing an original taxonomy of the major clinical trials' stakeholders and at reading them in the light of the competing interests of access, cost, and quality.

## CHAPTER FOUR: CLINICAL TRIALS ETHICS IN CONTEXT

### I. Introduction

Clinical trials raise several ethical concerns.<sup>184</sup> Those concerns become more intense in the case of global clinical trials.<sup>185</sup> While many within the scientific and legal literature have contributed to defining and testing the ethical rules that are relevant in the field of clinical trials, this contribution follows the seven ethical principles identified by Emanuel et al. in the renowned contribution “*What makes clinical research in developing countries ethical? The benchmarks of ethical research.*”<sup>186</sup> In particular, the eight ethical principles identified in the latter are the following: collaborative partnership, social value, scientific validity, fair selection of study population, favorable risk-benefit ration, independent review, informed consent, and respect for recruited participants and study communities.<sup>187</sup>

The next sections of this chapter will aim at (i) presenting concrete legal formulations in which the eight ethical principles could be “translated” and implemented into normative documents; (ii) when possible and appropriate, presenting examples of specific projects that follow (or are coherent with) the eight ethical principles; and (iii) expand the eight ethical principles suggesting how their “agenda” could be completed by the addition of an eight principle.

### II. Legal Formulas and Examples

The seven ethical principles identified by Emanuel et al. have the advantage of being comprehensive and concise. However, the article that introduced them does not provide

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<sup>184</sup> Cf. among others, Freedman, Benjamin. “Equipoise and the Ethics of Clinical Research.” *New England Journal of Medicine* (1987). Schafer, Arthur. “The Ethics of the Randomized Clinical Trial.” *New England Journal of Medicine* 307.12 (1982): 719-724. And Beecher, Henry K. “Ethics and Clinical Research.” *New England Journal of Medicine* 274.24 (1966): 1354-1360.

<sup>185</sup> Cf. among others, Varmus, Harold, and David Satcher. “Ethical Complexities of Conducting Research in Developing Countries.” (1997): 1003-1005. Shapiro, Harold T., and Eric M. Meslin. “Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries.” (2001): 139-142. Angell, *op. cit.* And Benatar, Solomon R. “Reflections and recommendations on research ethics in developing countries.” *Social Science & Medicine* 54.7 (2002): 1131-1141.

<sup>186</sup> Emanuel, et al. (2004) *op. cit.*

<sup>187</sup> *Ibid.*

for concrete indications as to how to translate them into specific legal provisions. For example, the principle of informed consent is acknowledged and affirmed but “only” four benchmarks – described as “practical measures” by the authors – are presented to the reader as explanatory tools; the four benchmarks suggest “involv[ing] the community in establishing recruitment procedures,” utilize “culturally appropriate” formats, etc. The same explanatory mechanism based on principles and benchmarks is used for the other six ethical principles.

However, the benchmarks are numerous (31 in total) and are expected to be balanced in a “process that requires judgment.”<sup>188</sup> This mechanism risks putting legislators in front of a balancing exercise that they may not be willing to conduct, and leaves them without a practical suggestion as to how to concretely implement such principles.

Therefore, the following paragraphs will try to present potential concrete formulations that legislators willing to fully implement the seven ethical principles could rely on. Some of the formulations are autonomously developed, while some are modeled on the basis of the findings of a National Bioethics Advisory Commission report (NBAC Report).<sup>189</sup>

Conscious of the fact that legislative reform requires widespread political support and that not every national legislator may have an interest in implementing such ethical principles, the following paragraphs will also try to provide the readers with some concrete examples of projects that have put in practice each of the ethical principles. Listing those examples may offer to clinical trials stakeholders (in particular, investigators and sponsors) inputs as of which aspects of their action could be improved and through which practices.

Therefore, the next paragraphs, for each of the seven principles, will first provide a description, second, provide a legal formulation that could be of interest for prospective legislators, and third, provide an example of practical implementation.

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<sup>188</sup> Ibid.

<sup>189</sup> US National Bioethics Advisory Commission (NBAC) Report (hereinafter: NBAC Report), available at:

<https://bioethicsarchive.georgetown.edu/nbac/clinical/execsum.html>

### *(1) Collaborative Partnership*

Collaborative partnership is the first ethical principle listed in Emanuel et al.'s contribution. This ethical principle is the most peculiar in the framework of global clinical trials conducted in developing countries, in fact, it is the only principle added by Emanuel et al. in the passage from the first contribution (i.e. "What Makes Clinical Research Ethical?")<sup>190</sup> to the second one (i.e. "What makes clinical research in developing countries ethical? The benchmarks of ethical research.")<sup>191</sup>

The explanatory benchmarks associated with this principle concern the development of partnerships that involve partners in sharing responsibilities (and benefits) and simultaneously ensure the respect of local cultures. Amongst the goals of the principle are: fostering mutual respect and minimizing disparities between the role, contribution, and profit-sharing of the partners based in developed economies and those based in the host country.<sup>192</sup> While many authors have addressed the topic of collaborative partnership, Lau et al. noted that the activity encompasses the need to assess needs and build sustainable capacity, to engage all stakeholders, to invest in leadership and strategic planning, and to practice cultural awareness.<sup>193</sup>

An example of collaborative partnership in global clinical trials fostered in part by private stakeholders is the Yale School of Medicine partnership to promote clinical trials and training in Puerto Rico.<sup>194</sup> The partnership provides for community training and shared services for multisite clinical trials in Puerto Rico.<sup>195</sup> Also, Yale-staff members, under the partnership agreement, will travel to Puerto Rico to provide support and training to local researchers and will perform monitoring of the Puerto Rican sites as needed.<sup>196</sup> Another example of collaborative partnership, established by private as well as institutional stakeholders on a larger scale is the European and Developing Countries

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<sup>190</sup> Emanuel, Ezekiel J., et al. (2000) *op. cit.*

<sup>191</sup> Emanuel, Ezekiel J., et al. (2004) *op. cit.*

<sup>192</sup> *Ibid.*

<sup>193</sup> Lau, Chuen-Yen, et al. "International Collaborative Research Partnerships: Blending Science with Management And Diplomacy." *Journal of AIDS & Clinical Research* 5.12 (2014).

<sup>194</sup> "Yale School of Medicine expands partnership to promote clinical trials and training in Puerto Rico." *YaleNews*, 18 July 2017, [news.yale.edu/2017/06/06/yale-school-medicine-expands-partnership-promote-clinical-trials-and-training-puerto-rico](https://news.yale.edu/2017/06/06/yale-school-medicine-expands-partnership-promote-clinical-trials-and-training-puerto-rico).

<sup>195</sup> *Ibid.*

<sup>196</sup> *Ibid.*

Clinical Trials Partnership.<sup>197</sup> Under the partnership, the EU will provide a contribution of up to € 683 million between 2014 and 2024 and the program involves 14 African and 14 European countries as full and equal members.<sup>198</sup> Both examples seem to respect and foster the ethical principle of collaborative partnership, especially to the extent that they involve partners in sharing responsibilities and promote the development of the capacity of local researchers.

One way in which legislators can support collaborative partnership is, for example, by providing support for the financial cost of compliance. Consistently with the NBAC Report's finding, countries willing to implement the ethical principle of collaborative partnership should include provisions in their legislation to "provide financial support for the administrative and operational cost of host country compliance with requirements of oversight of research involving human participants."<sup>199</sup>

## *(2) Social Value*

Social value is the second ethical principle listed in Emanuel et al.'s contribution. The principle is based on the notion that scientific research is rooted in the need to produce results that will benefit the community. This is especially true in a context in which social benefits for host countries take different shapes, varying from indirect medical benefits to payments for subjects and local investigators.<sup>200</sup> However, in the context of the ethical principle of social value, the main concern regards the need to specify who will benefit of the research and to connect it with the community that hosts any specific clinical trial.<sup>201</sup>

An example of private-actors action that follows those concerns can be found in the policy adopted by the pharmaceutical company GlaxoSmithKline (GSK). The latter,

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<sup>197</sup> European Commission, "Policies." European and Developing Countries Clinical Trials Partnership | Health - Research & Innovation - European Commission,

[ec.europa.eu/research/health/index.cfm?pg=policy&polycyname=edctp](http://ec.europa.eu/research/health/index.cfm?pg=policy&polycyname=edctp).

<sup>198</sup> Ibid.

<sup>199</sup> Cf. Recommendation 5.4, NBAC Report.

<sup>200</sup> Wenner, Danielle M. "The Social Value of Knowledge and International Clinical Research." *Developing World Bioethics* 15.2 (2015): 76-84.

<sup>201</sup> Cf. The four benchmarks connected with "Social value" in Emanuel, Ezekiel J., et al. (2004) *op. cit.*

when conducting global clinical trials that involve developing economies as hosts, pledges to respect the following rule:

“GSK-sponsored clinical trials are only conducted in countries where the medicines are likely to be suitable for the country’s wider community. Furthermore, clinical trials of investigational medicines are not conducted in countries when it is known at the outset that there is no intent to pursue registration and make the medicine available for use in that country.”<sup>202</sup>

In this context, GSK’s pledge can be seen as a positive attempt to respect the ethical principle of social value or at least to take into consideration the prospective value of research for the community hosting clinical trials. An additional and more concrete example of partnership that complies with the goal of respecting social value – and, specifically, with the goal of not supplanting local healthcare infrastructures – is the US-Liberia partnership, established during the Ebola outbreak in 2015.<sup>203</sup> The partnership makes global resources available locally and acknowledges the importance of not running operations that are completely foreign to the host-communities.<sup>204</sup>

Legislators willing to fully prevent private stakeholders from disregarding the ethical principle of social value could implement more precise provisions. For example, they could affirm that “clinical trials conducted in developing countries should be limited to those studies that are responsive to the health needs of the host county.”<sup>205</sup>

### (3) *Scientific Validity*

The third ethical principle identified by Emanuel et al. is scientific validity. In general, scientific validity deals with the design of the study – i.e. correct assessment and choice of randomisation, allocation concealment, blinding, and sample size – and with the

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<sup>202</sup> GSK Public policy positions, “*Clinical Trials in the Developing World*” – A publication of GlaxoSmithKline Communications and Government Affairs, January 2014, <https://www.gsk.com/media/2938/clinical-trials-in-the-developing-world-policy.pdf>

<sup>203</sup> “Liberia-U.S. Clinical Research Partnership Opens Trial to Test Ebola Treatments.” *National Institute of Allergy and Infectious Diseases*, U.S. Department of Health and Human Services, 17 Oct. 2017, [www.niaid.nih.gov/news-events/liberia-us-clinical-research-partnership-opens-trial-test-ebola-treatments](http://www.niaid.nih.gov/news-events/liberia-us-clinical-research-partnership-opens-trial-test-ebola-treatments).

<sup>204</sup> National Academies of Sciences, Engineering, and Medicine. *Integrating clinical research into epidemic response: the Ebola experience*. National Academies Press, 2017.

<sup>205</sup> Cf. Recommendation 1.3, NBAC Report. Note also Recommendation 4.2, NBAC Report, which reads as follows “Research proposals submitted to ethics review committees should include an explanation of how new interventions that are proven to be effective from the research will become available to some or all of the host country population beyond the research participants themselves. Where applicable, the investigator should describe any pre-research negotiations among sponsors, host country officials, and other appropriate parties aimed at making such interventions available (...)”

necessity for the trial to produce results that can be generalized to the prospective users' population.<sup>206</sup> In the context of global clinical trials, these concerns stand but are also coupled with concerns for the quality of the data produced.<sup>207</sup> Furthermore, additional specific concerns regard the goal of "guaranteeing research participants the health-care intervention to which they are entitled."<sup>208</sup> This issue falls within the widespread debate over the use of placebos in clinical trials conducted in developing countries. The controversy over the use of placebo treatments, in particular, concerns the practice of administering placebo treatments to subjects who, in developing countries, would not have had access to the treatment available for subjects in developed countries in any event, despite the existence, at a global level, of a best available treatment that could be administered as active-control.<sup>209</sup>

First, an example of project that focuses on the prevention of data falsification to comply with the ethical concern for scientific validity, concerns the use of blockchain protocols in clinical trials. Blockchain is the database connected with Bitcoins and other cryptocurrencies and promoters of its use in the context of healthcare claim that it could guarantee a better public-like supervision of data-entry in clinical trials, significantly reducing the risk of data inaccuracy and falsification.<sup>210</sup> Second, with regard to the use of placebo vs. active-control treatments, concrete cases of policies implemented by private stakeholders seem to be limited. For example, the pharmaceutical company Novartis pledged to always justify its choice of comparator (between placebo and active

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<sup>206</sup> Akobeng, Anthony K. "Assessing the Validity of Clinical Trials." *Journal of Pediatric Gastroenterology and Nutrition* 47.3 (2008): 277-282.

<sup>207</sup> Cf. George, Stephen L., and Marc Buyse. "Data Fraud in Clinical Trials." *Clinical Investigation* 5.2 (2015): 161 and – looking at recent "scandals" – Buranyi, Stephen, and Hannah Devlin. "Dozens of Recent Clinical Trials May Contain Wrong or Falsified Data, Claims Study." *The Guardian*, Guardian News and Media, 5 June 2017, [www.theguardian.com/science/2017/jun/05/dozens-of-recent-clinical-trials-contain-wrong-or-falsified-data-claims-study](http://www.theguardian.com/science/2017/jun/05/dozens-of-recent-clinical-trials-contain-wrong-or-falsified-data-claims-study).

<sup>208</sup> Emanuel, et al. (2004) *op cit*.

<sup>209</sup> Cf. Brody, Howard. "Placebos and the Philosophy of Medicine Clinical, Conceptual, and Ethical Issues." (1980). Lurie, Peter, and Sidney M. Wolfe. "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries." *New England Journal of Medicine* 337.12 (1997): 853-6. And Bhutta, Zulfiqar A. "Ethics in International Health Research: A Perspective from the Developing World." *Bulletin of the World Health Organization* 80.2 (2002): 114-120.

<sup>210</sup> "Better with bitcoin." *The Economist*, 21 May 2016,

[www.economist.com/news/science-and-technology/21699099-blockchain-technology-could-improve-reliability-medical-trials-better](http://www.economist.com/news/science-and-technology/21699099-blockchain-technology-could-improve-reliability-medical-trials-better). And Nugent, Timothy, David Upton, and Mihai Cimpoesu. "Improving data transparency in clinical trials using blockchain smart contracts." *F1000Research* 5 (2016).

treatment) on both scientific and ethical grounds.<sup>211</sup> However, policies of this kind do not specify how the balance between scientific and ethical concerns ought to be conducted.

Therefore, it seems particularly important to promote the implementation of clear legislative standards in this context. Some institutional commentators suggest that placebo-controlled trials should be completely banned.<sup>212</sup> However, given that placebo-controlled trials may be acceptable or useful under certain scientific considerations,<sup>213</sup> a ban on placebo-treatments *per se* may set a standard that would stray too far from the needs and expectations of the scientific community and sponsors of major clinical trials. Nevertheless, to prevent different local standards of care from being the decisive factor in choosing how to conduct clinical trials, uniform standards should be considered, independently from the location. A norm implemented to fulfill this goal could read as follows: “Clinical trials participants assigned to a control-group shall be provided with the best available active treatment, independently from whether the latter is available as default option in the host country.”<sup>214</sup> Legislators willing to provide for an exception to the rule should add formulae consistent with that stated in Recommendation 2.2 in the NBAC Report i.e. “[a]ny study that would not provide the control group with an established effective treatment should include a justification for using an alternative design. Ethics review committees must assess the justification provided, including the risk to participants, and the overall ethical acceptability of the study design.”<sup>215</sup>

#### *(4) Fair Selection of Study Population*

The fourth ethical principle listed by Emanuel et al. is the fair selection of the study population. The principle, as the benchmarks associated with it suggest, derives from two kinds of concerns: first, the one for selecting the study population “to ensure scientific

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<sup>211</sup> Novartis Public Affairs, “Novartis Position on Clinical Trials in Developing Countries”, August 2011, <https://www.novartis.com/sites/www.novartis.com/files/clinical-trials-developing-markets.pdf>

<sup>212</sup> See, for example, the report “Clinical trials in developing countries and Swissmedic’s role in protecting vulnerable participants” edited by the Berne Declaration, an independent Swiss non-governmental organization, [https://www.publiceye.ch/fileadmin/files/documents/Gesundheit/1309\\_SWISSMEDIC\\_Final\\_Report\\_ENG.pdf](https://www.publiceye.ch/fileadmin/files/documents/Gesundheit/1309_SWISSMEDIC_Final_Report_ENG.pdf)

<sup>213</sup> Temple and Ellenberg, *op. cit.*

<sup>214</sup> Cf. Recommendation 2.2, NBAC Report.

<sup>215</sup> *Ibid.*

validity of the research”<sup>216</sup> and, second, the one for the protection of vulnerable populations that have traditionally been subjected to high-risk research studies.<sup>217</sup> The first concern has been addressed within the section dedicated to scientific validity in this contribution. The second concern, however, remains at the core of the “fair selection of study population” ethical principle. In that context, the identification of vulnerable populations in developing and developed countries has vastly overlapping results. In fact, in both cases, a broad definition of vulnerable subjects can be seen as including the following categories of subjects: children, pregnant women, prisoners, terminally ill, physically and intellectually challenged individuals, institutionalized individuals, elderly individuals, and ethnic minorities.<sup>218</sup> Concerns for those subjects’ participation in clinical trials regard mainly the risk of coercion and non-autonomous informed consent decision-making.<sup>219</sup>

In the context of fair selection (and above all, treatment) of study population, two examples seem to be particularly interesting. The first one regards the role of potentially vulnerable populations and their involvement in the evaluation of the ethical challenges connected with clinical research. The project – called TRUST – involves 13 international partners and aims at generating an online tool for “fair research contracting.”<sup>220</sup> Its role – among others – will be to provide standard contracts that vulnerable communities will be able to access at no cost to better negotiate their involvement in scientific research.<sup>221</sup> Furthermore, as a concrete result of TRUST’s efforts, local indigenous communities have already been supported in drafting specific ethical codes to specify their position towards clinical trials conducting in their local community.<sup>222</sup> The second example of a specific project adopted to better achieve full compliance with the ethical principle of fair selection of study population, with a specific focus on the protection of vulnerable

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<sup>216</sup> Emanuel, et al. (2004) *op cit*.

<sup>217</sup> *Ibid*.

<sup>218</sup> Shivayogi, Preethi. “Vulnerable Population and Methods for Their Safeguard.” *Perspectives in Clinical Research* 4.1 (2013): 53.

<sup>219</sup> *Ibid*.

<sup>220</sup> Kate Chatfield. “The Ethics of Research: How to End the Exploitation of Vulnerable Communities.” *The Conversation*, 22 Oct. 2017, [theconversation.com/the-ethics-of-research-how-to-end-the-exploitation-of-vulnerable-communities-74203](http://theconversation.com/the-ethics-of-research-how-to-end-the-exploitation-of-vulnerable-communities-74203).

<sup>221</sup> *Ibid*.

<sup>222</sup> This is the case of three South African San groups that have developed a Code of Research Ethics, aligned with their own values. *Ibid*.

subjects in the informed-consent phase, is the Global Health Trials website. The latter is part of a wider set of projects which have received conspicuous funding from the Bill and Melinda Gates Foundation starting in 2010.<sup>223</sup> Concretely, the website provides free access to a variety of templates for e.g. informed consent forms, which researchers that have already worked in developing countries can share with both researchers based in developed countries planning to conduct global clinical trials and researchers based in host developing countries.<sup>224</sup>

As to the possible steps that legislators willing to protect the ethical principle of fair selection of study population and, specifically, to implement rules that will better protect vulnerable subjects in the informed-consent phase, two insights can be provided. The first regards the possibility to implement a broad set of norms to establish a protection mechanism. Hurst developed a comprehensive analysis of the fragmented legal and ethical standards applicable to those subjects, but also highlighted how it is possible to address vulnerability through a four-step process.<sup>225</sup> The steps require: (i) identifying the presence of a potential risk; (ii) assessing whether the risk-rate is higher in the case of some portions of the population; (iii) identifying who shares the duty to minimize such risk; and (iv) assessing how the risk can be minimized.<sup>226</sup> Possibly, to overcome the risk of an impasse related to the difficulty in prospectively listing vulnerable subjects in normative documents, legislators should consider asking subjects who apply to conduct clinical trials to present an answer to the four above-listed questions.

The second consideration is more specific and regards the suggestion to implement in normative documents specific provisions aimed at containing the risks connected with the participation of subjects that are arguably vulnerable. In this context, provisions could be established on the basis of two concerns: the role of community representatives in the process of acquiring informed consent and the risk of coercion in subjects' recruitment and acquisition of informed consent. Following the first concern, a provision similar to the following could be implemented: "sponsors and investigators shall be sensitive to

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<sup>223</sup> Nature America, "Website pools clinical trial forms for use in developing countries", 2014  
<https://www.nature.com/nm/journal/v20/n7/pdf/nm0714-694.pdf?origin=ppub>

<sup>224</sup> Ibid.

<sup>225</sup> Hurst, Samia A. "Vulnerability in Research and Health Care; Describing the Elephant in the Room?" *Bioethics* 22.4 (2008): 191-202.

<sup>226</sup> Ibid.

local customs requiring that a local community representative gives permission to approach perspective participants.”<sup>227</sup> The rule should, however, be balanced, by taking into consideration the second concern. Hence, a complementary rule should be implemented entailing that “sponsors and investigators shall ensure that individuals agree to participate in research without coercion or undue inducement from community representatives.”<sup>228</sup>

#### *(5) Favorable Risk-Benefit ratio*

The fifth ethical principle listed by Emanuel et al. is the presence of a favorable risk-benefit ratio. In general, the latter refers to a balance in which the benefits for participants outweigh the risks.<sup>229</sup> Traditionally, the benefits associated with the participation in clinical trials regard the fact that participants will be given access to the new treatment or – at least – to a standard-treatment, to medical supervision, and to the possibility to contribute to the advancement of scientific knowledge.<sup>230</sup> On the other hand, the risks associated with the participation in clinical trials encompass the material and psychological cost of participating and the fact that the tested treatment may not result to be “better than the current standard care” and may present side effects.<sup>231</sup>

The three core goals in the risk-benefit ratio evaluation are quality, consistency, and transparency of the assessment.<sup>232</sup> A concrete way in which sponsors and investigators can quantify and convey the risk-benefit ratio associated with any clinical trial entail the choice and mastering of a descriptive or quantitative framework. Describing such frameworks – which, in substance, represent protocols for the definition and description

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<sup>227</sup> Cf. Recommendation 3.6, NBAC Report.

<sup>228</sup> Cf. Recommendation 3.7, NBAC Report.

<sup>229</sup> Emanuel, et al. (2004) *op cit*.

<sup>230</sup> See, for example, “What Are the Possible Benefits and Risks of Clinical Trials?” *National Heart Lung and Blood Institute*, US Department of Health and Human Services, [www.nhlbi.nih.gov/studies/clinicaltrials/benefitsrisks](http://www.nhlbi.nih.gov/studies/clinicaltrials/benefitsrisks). “Benefits and risks of clinical trials - Canadian Cancer Society.” [www.cancer.ca/en/cancer-information/diagnosis-and-treatment/clinical-trials/benefits-and-risks-of-clinical-trials/?region=on](http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/clinical-trials/benefits-and-risks-of-clinical-trials/?region=on). And National Health and Medical Research Council and Department of Industry and Science. “Potential benefits and risks.” *National Health and Medical Research Council and Department of Industry and Science*, 17 Feb. 2015, [www.australianclinicaltrials.gov.au/why-be-part-clinical-trial/potential-benefits-and-potential-risks](http://www.australianclinicaltrials.gov.au/why-be-part-clinical-trial/potential-benefits-and-potential-risks).

<sup>231</sup> Van Luijn, H. E. M., et al. “The Evaluation of the Risks and Benefits of Phase II Cancer Clinical Trials by Institutional Review Board (IRB) Members: A Case Study.” *Journal of Medical Ethics* 32.3 (2006): 170-176.

<sup>232</sup> Stephen J. Mayall, Anjan K. Banerjee, “Benefit–risk Assessment and Public Communication.” *Therapeutic Risk Management of Medicines* (2014) 335–357.

of the risk and benefit balance in any clinical trial – goes beyond the scope of this contribution. However, by way of an example, it can be noted that at least eight descriptive frameworks<sup>233</sup> and nine quantitative frameworks<sup>234</sup> exist and that it may be beneficial for to prospectively identify which framework on which they wish sponsors and investigators to rely.

Provisions aimed at increasing transparency in the context of the risk-benefit ratio assessment could read as follows: “Sponsors and investigators should present and justify the research design to be used, including the consistent description and application of (i) the descriptive and quantitative protocols and (ii) the procedures to be used to assess and minimize risks to participants.”<sup>235</sup> Furthermore, looking at which provisions could be implemented taking into consideration concerns related specifically to the case of global clinical trials conducted in developing countries, the recourse to the ethical principle of favorable risk-benefit ratio could be used to supplement the rules suggested in the context of the ethical principle of social value (addressed earlier). Hence, for example, legislators should consider implementing corollary provisions similar to last part of Recommendation 4.2 of the NBAC Report, which reads as follows: “In cases in which investigators do not believe that successful interventions will become available to the host country population, they should explain to the relevant ethics review committee(s) why the research is nonetheless responsive to the health needs of the country and presents a reasonable risk/benefit ratio.”<sup>236</sup>

#### *(6) Independent Review*

Independent review is the sixth ethical principle listed by Emmanuel et al. The general concerns behind such an ethical principle are the need to identify potential conflicts of

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<sup>233</sup> The eight descriptive frameworks are: ProACT-URL, BRAT (Benefit-Risk Action Team), ASF (Ashby and Smith Framework), CMR-CASS, COBRA (Consortium on Benefit-Risk Assessment), FDA BRF (the US FDA Benefit-Risk Framework), SABRE (Southeast Asia Benefit-Risk Evaluation), and UMBRA (Unified Methodologies for Benefit-Risk Assessment). A description of such protocols is provided in *PROTECT Benefit-Risk*, [protectbenefitrisk.eu/framework.html](http://protectbenefitrisk.eu/framework.html).

<sup>234</sup> The nine quantitative frameworks are: MCDA (Multi-Criteria Decision Analysis), SMAA (Stochastic Multi-attribute Acceptability Analysis), Decision Tree, MDP (Markov Decision Process), BLRA, Net Clinical Benefit, SBRAM (Sarac’s Benefit-Risk Assessment Method), CUI (Clinical Utility Index), and DI (Desirability Index). A description of such protocols is provided in *PROTECT Benefit-Risk*, [protectbenefitrisk.eu/framework.html](http://protectbenefitrisk.eu/framework.html).

<sup>235</sup> Cf. Recommendation 2.1, NBAC Report.

<sup>236</sup> Cf. Recommendation 4.2, NBAC Report.

interests and to foster public accountability.<sup>237</sup> More specifically, the benchmarks associated with the ethical principle of independent review regard the need to ensure independence, competence, and public accountability of the reviews.<sup>238</sup> Although this does not amount to an example of best practice in the field of independent review, it can be noted that recently a tendency has developed under which for-profit review boards are taking over for hospitals, at least in the US market.<sup>239</sup>

As for the concrete provisions that a legislator may implement – especially in the context of the regulation of global clinical trials – some remarks can be presented. First, approval to clinical trials should be granted only following a prior ethical review conducted by an ethical committee. Second, such a review should take into consideration all the ethical principles analyzed so far in this contribution, as well as those that will be addressed in the following sections. Third, focusing specifically on the case of global trials a double ethical review system should be established. Hence, legislators should require clinical trials to “receive prior approval by both an ethical review committee based in their country and in the host country, unless the ethical review mechanism of the host country is found to respect the same principles and procedures of their one.”<sup>240</sup>

#### *(7) Informed Consent*

Informed consent is the seventh ethical principle identified by Emanuel et al. Informed consent is an issue transversal to all eight ethical principles because it is often in the informed-consent phase that the human subjects’ freedom of choice is protected. The benchmarks connected with this ethical principle deal with the need to involve local communities in establishing recruitment procedures, the need to utilize the most appropriate formats, and the need to ensure freedom to withdraw from clinical trials. Given the multiple issues connected with informed consent, the section about the fair selection of study participants (above in this contribution) has already partially touched

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<sup>237</sup> Emanuel, et al. (2004) *op cit.*

<sup>238</sup> Emanuel, et al. (2004) *op cit.*

<sup>239</sup> In mid-2016, commercial institutional review boards now oversaw an estimated 70 percent of US clinical trials, as noted in “In clinical trials, for-Profit review boards staged a revolution.” *STAT*, 6 July 2016, [www.statnews.com/2016/07/06/institutional-review-boards-commercial-irbs/](http://www.statnews.com/2016/07/06/institutional-review-boards-commercial-irbs/).

<sup>240</sup> Cf. Recommendation 5.2, NBAC Report.

on it. Nevertheless, it is important to highlight that the aim of informed consent is to acquire a voluntary consent based on a solid understanding of information.<sup>241</sup>

As of the current status of informed consent as an ethical principle in the context of global clinical trials, it can be noted that, following the strand of litigation tied to the Pfizer scandal regarding the trials conducted in Kano (Nigeria)<sup>242</sup> some commentators suggest that the informed consent requirement is sufficiently “(i) universal and obligatory, (ii) specific and definable, and (iii) of mutual concern,” to be considered a customary international law norm.<sup>243</sup>

On the one hand, practical examples of effective means to administer informed consent procedures encompass tailoring informed consent forms to the sex and developmental age of prospective participants, while associating counseling to traditional formal procedures.<sup>244</sup> Furthermore, a common recommendation regards the use of social language and the involvement of local leaders, when useful.<sup>245</sup> In this context, the Global Health Trials website described in the “fair selection of study participants” section of this contribution may represent a useful tool.<sup>246</sup>

On the other hand, legislators willing to introduce measures to protect and implement the ethical principle of informed consent should consider introducing the following provisions. First, clinical trials shall not be approved, unless they recruit participants on the basis of their voluntary informed consent. Second, “researchers shall adopt culturally appropriate ways to disclose information that is necessary for adherence to the substantive ethical standard of informed consent and shall describe in their protocols and justify to the ethics review committee(s) the procedures they plan to use for disclosing such information to participants.”<sup>247</sup> Third, “in order to obtain participants’ informed

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<sup>241</sup> Cf. Hyder, Adnan A., and Salman A. Wali. “Informed Consent and Collaborative Research: Perspectives from the Developing World.” *Developing World Bioethics* 6.1 (2006): 33-40. Angell, *op. cit.* And – for a more specific case – Mystakidou, et al. *op. cit.*

<sup>242</sup> *The Washington Post*, WP Company, Where Profits and Lives Hang in Balance, Joe Stephens, 2000, [www.washingtonpost.com/wp-dyn/content/story/2008/10/01/ST2008100101390.html](http://www.washingtonpost.com/wp-dyn/content/story/2008/10/01/ST2008100101390.html).

<sup>243</sup> *Abdullahi v. Pfizer, Inc.*, 562 F.3d 163 as discussed in Annas, George J. “Globalized Clinical Trials and Informed Consent.” *New England Journal of Medicine* 360.20 (2009): 2050-2053.

<sup>244</sup> Mystakidou, et al. *op. cit.*

<sup>245</sup> *Ibid.*

<sup>246</sup> Nature America, “*Website pools clinical trial forms for use in developing countries*” 2014 <https://www.nature.com/nm/journal/v20/n7/pdf/nm0714-694.pdf?origin=ppub>

<sup>247</sup> Cf. Recommendation 3.2, NBAC Report.

consent, researchers shall present – both to ethics review committees, prospectively, and prospective participants, on-site – information about benefits available to participants when the participation in the study has ended.”<sup>248</sup>

*(8) Respect for Recruitment Participants and Study Communities*

The eighth and final ethical principle identified by Emanuel et al. focuses on the respect for host study communities in which participants are recruited. It focuses on the conduct of researchers following the obtainment of informed consent.<sup>249</sup> There are five benchmarks connected with this ethical principle and they principally regard goals such as the protection of confidentiality of enrolled participants, and the right to withdraw from clinical trials, the divulgence of information that arises during clinical trials to participants and to their community.<sup>250</sup> Common practices associated with the achievement of these goals encompass the development of consistent contacts between the research staff and participants, the scheduling of numerous updates for contacting participants about progress, and the encouragement of contacts from participants and their community.<sup>251</sup>

Examples of private commitments to achieve the implementation of the ethical principle of respect for recruitment participants and study communities include the pledge presented by the pharmaceutical company Roche. The latter affirms its intention to keep the records of its clinical trials confidential and protected from disclosure to third parties also after the conclusion of the studies. In addition, it is committed to “provide the investigational medicinal product free for the duration of the study” and “continued access to the investigational medicinal product that they [participants] received after trial completion, when appropriate.”<sup>252</sup> Furthermore, private stakeholders willing to comply with the benchmark related to the need to communicate with patients and their

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<sup>248</sup> Cf. Recommendation 3.3, NBAC Report.

<sup>249</sup> Emanuel, et al. (2004) *op cit.*

<sup>250</sup> Emanuel, et al. (2004) *op cit.*

<sup>251</sup> See, for example, “Clearly Communicating Research Results across the Clinical Trials Continuum.” *National Institutes of Health*, US Department of Health and Human Services, 5 Oct. 2016, [www.nih.gov/health-information/nih-clinical-research-trials-you/clearly-communicating-research-results-across-clinical-trials-continuum](http://www.nih.gov/health-information/nih-clinical-research-trials-you/clearly-communicating-research-results-across-clinical-trials-continuum).

<sup>252</sup> “What is a Clinical Trial and How Does a Trial Work?” *Roche*,

[www.roche.com/research\\_and\\_development/who\\_we\\_are\\_how\\_we\\_work/clinical\\_trials/what\\_is\\_a\\_clinical\\_trial.htm?tab\\_id=tab10](http://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/what_is_a_clinical_trial.htm?tab_id=tab10).

communities have access to a variety of services available on the market; for example, PAREXEL’s Clinical Communications group – which, inter alia, has recently become a partner of Microsoft in the field of clinical trials services<sup>253</sup> – develops contents uniquely tailored to diverse audiences that sponsors and investigators can use both before and after the recruitment of participants.<sup>254</sup>

Legal formulae that legislators may want to introduce to protect and foster the ethical principle of respect for recruitment participants and study communities in context of global clinical trials, for example, could read as follows: “Sponsors and investigators shall consult with community representatives to establish effective means to communicate necessary information in a manner that is understandable to prospective participants – before recruitment –, to enrolled participants – following recruitment –, and their community.”<sup>255</sup> Consistently with the NBAC Report’s Recommendation 3.5, in case of lack of involvement of community representatives, “the protocol presented to the ethics review committee should justify why such involvement is not possible or relevant.”<sup>256</sup>

### III. Expanding Emanuel et al.’s Ethical Principles

From the perspective of this contribution, the ethical principles identified by Emanuel et al. are extremely helpful in orienting the everyday action of clinical trials stakeholders and the regulatory efforts of legislators. However, the list does not provide stakeholders or legislators with an additional principle as to how to allocate the responsibility to comply with such principles. Therefore, it seems appropriate and useful to include a ninth principle to accompany the eight ethical principles described above and better support their implementation: the principle of subsidiarity.

To present the suggestion regarding the inclusion of the principle of subsidiarity as ninth principle – and corollary principle – to the eight discussed in Emanuel et al., the following

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<sup>253</sup> “Microsoft and PAREXEL form Cloud Technology Alliance Aimed at Accelerating the Pace of Drug Development.” *Business Insider*, Business Insider, [markets.businessinsider.com/news/stocks/Microsoft-and-PAREXEL-form-cloud-technology-alliance-aimed-at-accelerating-the-pace-of-drug-development-1005448309](https://markets.businessinsider.com/news/stocks/Microsoft-and-PAREXEL-form-cloud-technology-alliance-aimed-at-accelerating-the-pace-of-drug-development-1005448309).

<sup>254</sup> “Global Study Engagement.” *PAREXEL*, [www.parexel.com/solutions/access/medical-communications-services/clinical-communications](http://www.parexel.com/solutions/access/medical-communications-services/clinical-communications).

<sup>255</sup> Cf. Recommendation 5.2, NBAC Report.

<sup>256</sup> *Ibid.*

paragraphs will address the following issues: (i) the definition of subsidiarity, (ii) why the principle can be considered also as an ethical tool, (iii) why the principle should be considered as relevant in the ethical discourse about clinical trials, (iv) how the principle can be usefully applied in the field of clinical trials (ethical) regulation, and (v) the limitations of the suggestion here presented and how they can be addressed.

(i) Subsidiarity is a principle used to assess how to allocate decision-making powers among different actors. According to the principle of subsidiarity, decision-making powers should be exercised at the lowest level of governance, provided that their exercise is equally effective.<sup>257</sup> In the international framework, it is mainly utilized in the allocation of powers in the context of the EU,<sup>258</sup> but its value in the field of international law and human rights is often discussed.<sup>259</sup> Notably, subsidiarity has a two-fold application, namely vertical (between different institutional levels) and horizontal (between different actors, institutional and non-institutional, at the same level).<sup>260</sup> These are the two applications on which the following paragraphs will rely. It is worth noting that in the specific context of scientific research, subsidiarity is and has been utilized also with a different meaning; this meaning utilizes subsidiarity to assess *when* scientific experiments should be conducted.<sup>261</sup> This contribution will not discuss such possible application of the principle of subsidiarity; instead, it will focus on the value of

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<sup>257</sup> Feichtner, Isabel. "Subsidiarity." *Oxford Public International Law*, 6 June 2017,

[opil.ouplaw.com/view/10.1093/law:epil/9780199231690/law-9780199231690-e1477?rskey=CFTYtA&result=1&prd=EPIL](http://opil.ouplaw.com/view/10.1093/law:epil/9780199231690/law-9780199231690-e1477?rskey=CFTYtA&result=1&prd=EPIL) and "EUR-Lex Access to European Union law." *Glossary of summaries - EUR-Lex*, [eur-lex.europa.eu/summary/glossary/subsidiarity.html](http://eur-lex.europa.eu/summary/glossary/subsidiarity.html).

<sup>258</sup> In the context of the EU, specifically, subsidiarity is "the principle whereby the EU does not take action (except in the areas that fall within its exclusive competence), unless it is more effective than action taken at national, regional or local level. It is closely bound up with the principle of proportionality, which requires that any action by the EU should not go beyond what is necessary to achieve the objectives of the Treaties." *Glossary of summaries - EUR-Lex*, *op. cit.*

<sup>259</sup> See, among others, Carozza, Paolo G. "Subsidiarity as a Structural Principle of International Human Rights Law." *American Journal of International Law* 97.1 (2003): 38-79. Alvarez, José E. *International organizations as Law-makers*. vol. 586 (Oxford University Press, 2005). And Kumm, Matthias. "The Legitimacy of International Law: a Constitutionalist Framework of Analysis." *European Journal of International Law* 15.5 (2004): 907-931.

<sup>260</sup> Feichtner, *op. cit.*

<sup>261</sup> See, for example, the application of the principle of subsidiarity to the subsidiarity principle to establish that "research on embryos should only be conducted if no suitable alternatives exist." Pennings, Guido, and André Van Steirteghem. "The Subsidiarity Principle in the Context Of Embryonic Stem Cell Research." *Human Reproduction* 19.5 (2004): 1060-1064.

subsidiarity in its more traditional legal meaning, as a principle to assess *how* to allocate decision-making powers in the field of clinical trials.

(ii) Subsidiarity, in the context of this contribution, is relied upon not solely for its legal value but also for its ethical one. In fact, subsidiarity can be seen not only as a mechanism to regulate the allocation of power, but also as a cooperative principle. As suggested by Carozza, subsidiarity also represents the “principle that each social and political group should help smaller or more local ones accomplish their respective ends without, however arrogating those tasks to itself.”<sup>262</sup> Therefore, subsidiarity can also be seen as a corollary value that could accompany a better protection and implementation of the rights of human subjects, to the extent that it hands such protection and implementation to a clear institutional subject on the basis of the appropriateness of its action and the interest of citizens therein.

(iii) Furthermore, the application of the principle of subsidiarity in the specific context of clinical trials regulation would be particularly useful, considering the globalization through which the clinical trials framework is currently evolving. In this context, national legislation can do much to affect clinical trials, but their global dimension often reduces the impact of national norms alone can have. At the same time, some specific aspects of the implementation of clinical trials standards – even when they have an international nature and scope – cannot be managed solely at the international level. Hence, keeping in mind the goal of fully implementing the eight ethical principles identified by Emanuel et al., reliance on the principle of subsidiarity could guarantee a more effective development and implementation of clinical trials regulation.

(iv) Specifically, the principle of subsidiarity could be applied in the context of clinical trials regulation on three levels. To follow the structure chosen by Emanuel et al., these three levels could be seen as representing the three benchmarks associated with the principle. In particular, the three levels can be described as: (a) horizontal subsidiarity – to better assess whether an issue can be better addressed through the private action of the stakeholders (sponsors, investigators, human subjects) or through the public action of institutions; (b) sub-horizontal subsidiarity – when the issue can be better addressed through the private action of the stakeholders and there is a need to assess which category

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<sup>262</sup> Carozza, *op. cit.*

of stakeholders can better address it (e.g. sponsors, investigators, and/or human subjects); and (c) vertical subsidiarity – when the issue can be better addressed through the public action of institutions and there is a need to assess which level of power should have the competence to act (e.g. supra-national level, national level, local-community level, etc.). Examples of how the mechanism provided by the principle of subsidiarity could represent a necessary and structural corollary of the eight ethical principles listed by Emanuel et al., can be easily identified. For example, first, one of the benchmarks associated with the ethical principle of fair selection of study population is “select the study population to ensure scientific validity of the research.”<sup>263</sup> With the latter being such a concrete issue, it is likely that applying horizontal subsidiarity would bring the conclusion that private stakeholders are the actors that could more effectively implement the benchmark. Applying sub-horizontal subsidiarity may then result in the identification of sponsors as investigators as the two stakeholders with a higher chance of effectively protecting the benchmark. Second, one of the benchmarks associated with the ethical principle of social value is to “prevent supplanting the extant health system infrastructure and services.”<sup>264</sup> Given that healthcare is a matter that relies mainly on decisions taken at the national level, applying horizontal subsidiarity as well as vertical subsidiarity may result in the allocation of the decision-making power in the context of the protection of that aspect of social value to national governments. Third, similarly, the protection and implementation of the benchmark “disclose information in culturally and linguistically appropriate formats,” associated with the “informed consent” ethical principle,<sup>265</sup> may effectively be left to the level of the local community, following the application of vertical subsidiarity. Fourth and finally, decision-making powers regarding the benchmark “ensure public accountability through transparency and review by other international and nongovernmental bodies, as appropriate,” associated with the “independent review” ethical principle,<sup>266</sup> would be better exercised if allocated to the international level (e.g. to the WHO).

(v) Finally, it is worth noting that some shortcomings may affect the current expansion of the model ideated by Emanuel et al. The most valuable concern regards the possibility

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<sup>263</sup> Feichtner, *op. cit.*

<sup>264</sup> Emanuel, et al. (2004) *op cit.*

<sup>265</sup> *Ibid.*

<sup>266</sup> *Ibid.*

that the principle of subsidiarity, applied alone, would guarantee a completely successful implementation of the other eight ethical principles. A possible way of addressing such concerns could entail the inclusion of other three principles next to the subsidiarity one – either as autonomous expansions of the eight original principles or as benchmarks associated with the subsidiarity principle. The three additional principles could represent some of the core principles at the base of the international legal system i.e. the principle of international legality, the principle of adequate participation and accountability, and the principle of achieving outcomes that are not violative of fundamental rights and are reasonable.<sup>267</sup>

#### IV. Preliminary Conclusions

This contribution has built on the cornerstone findings of leading authors in the area. In particular, first, it identified and presented examples of best practices with regard to the protection and implementation of the eight ethical principles listed by Emanuel et al. This activity aimed at clarifying what the eight principles may signify in concrete terms as well as at providing private stakeholders with examples of ways in which they can impact the respect of ethical principles in their daily activity. Second, it provided some legal formulae that legislators might consider implementing when regulating clinical trials in accordance with the eight ethical principles. Third, it suggested a possible expansion of the model established by Emanuel et al. Such an expansion focuses on the addition of a ninth principle – the principle of subsidiary – which represents a necessary and structural element for the full and effective implementation and protection of the other eight principles.

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<sup>267</sup> For the identification of the principles see Kumm, *op. cit.*

## CHAPTER FIVE: COMPARATIVE ANALYSIS – CLINICAL TRIALS REGULATION IN THE EUROPEAN UNION AND THE UNITED STATES

### I. Introduction

This chapter presents a comparative analysis of the EU and US clinical trial legal frameworks. The aim of such analysis is twofold: to identify points of contacts and similarities in the two sets of provisions and to detect divergences and differences between the two systems. This exercise will provide: (i) in terms of policy – for national and international legislators –, useful insights in terms of assessment of the standards applicable in two of the most advanced clinical trials legal frameworks (that often serve as models for other legal systems); and (ii) in terms of compliance – for actors willing to operate under both legal frameworks –, detailed information about the most challenging differences between the two systems. In this context, it is worth noting that a comparative analysis of the size proposed in this contribution does not already exist in the literature. Furthermore, the conclusions presented here are particularly original as one of the main items taken here into consideration is a recent EU legislative document, which has not yet been the object of extensive analysis.

The main sources for the regulation of clinical trials taken into consideration in this contribution are the following: for clinical trials in the EU legal framework, Regulation No. 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use (the “Clinical Trials Regulation,” hereinafter: EU CTR), adopted on 16 April 2014 and published in the Official Journal on 27 May of the same year.<sup>268</sup> Due to some delays, the Regulation is not yet in force; it is expected to come into full application in 2019.<sup>269</sup> Until then, Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the

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<sup>268</sup> 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 (Text with EEA relevance). Hereinafter within the references “EU CTR 536/2014.”

<sup>269</sup> “Clinical Trial Regulation.” European Medicines Agency - Clinical trials - Clinical Trial Regulation, [www.ema.europa.eu/ema/index.jsp?curl=pages%2Fregulation%2Fgeneral%2Fgeneral\\_content\\_000629.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fregulation%2Fgeneral%2Fgeneral_content_000629.jsp).

implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (the “Clinical Trials Directive”) will still apply. However, this contribution will not focus on it – both because being a directive it includes less specific and directly applicable obligations than the Clinical Trials Regulation, and because it is nevertheless destined to lose its legal value and relevance in the short term.

For clinical trials in the US legal framework, a variety of sources are relevant. We might begin with the Code of Federal Regulations (hereinafter: US CFR), as it has been dubbed “the codification of the general and permanent rules published in the Federal Register by the departments and agencies of the Federal Government produced by the Office of the Federal Register (OFR) and the Government Publishing Office.”<sup>270</sup> In particular, the most relevant provisions taken into consideration belong to Title 45 US CFR 46 (The Common Rule) which is a core set of regulations defining protection of Human Subjects in clinical research;<sup>271</sup> and to Title 21 US CFR, which applies when research is being conducted to develop a medical product that will be licensed for sale in the US.<sup>272</sup>

With regard to international standards and guidelines, documents that will be taken into consideration, when appropriate, include, for example, the guidelines produced by the International Conference on Harmonisation (ICH).

## II. Comparative analysis

As noted above, the core aim of this chapter is to build a comparative analysis of the EU and US clinical trial legal frameworks. In order to achieve this aim, the next sub-sections will focus on five specific clinical trials aspects that both legal frameworks address and regulate. First, the fundamental preliminary elements established in clinical trials regulations. Second, the scope and technical aspects of the applications that sponsors are required to submit to governmental authorities in order to obtain an authorization to conduct clinical trials in the EU or in the US territories – or outside such territories, but

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<sup>270</sup> *ECFR — Code of Federal Regulations*, US Government Publishing Office, [www.ecfr.gov/cgi-bin/ECFR?page=browse](http://www.ecfr.gov/cgi-bin/ECFR?page=browse).

<sup>271</sup> “How Is Clinical Research Governed?” *Duke School of Medicine*, [medschool.duke.edu/research/clinical-and-translational-research/duke-office-clinical-research/about-clinical-research-0](http://medschool.duke.edu/research/clinical-and-translational-research/duke-office-clinical-research/about-clinical-research-0).

<sup>272</sup> *Ibid.* And Center for Devices and Radiological Health. “Medical Device Databases - Code of Federal Regulations - Title 21 - Food and Drugs.” *US Food and Drug Administration Home Page*, Center for Devices and Radiological Health, [www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/ucm135680.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/ucm135680.htm).

subject to the EU or US legal standards. Third, the mechanisms on the basis of which such applications for authorization are scrutinized in each system. Fourth, some specific concerns that both legislators address in their clinical trials-related provisions – such concerns are *de facto* addressed when applications are assessed, but given the fact that they particularly focus on concerns connected with the protection of human subjects in clinical trials, they are analyzed here in a dedicated sub-section. Finally, fifth, the ways in which the EU and the US systems regulate the monitoring of approved clinical trials.

### *(1) Fundamental Elements*

This section will present the fundamental elements established in the EU and US legal frameworks on the matter of clinical trials regulation. Their identification and description is propaedeutic to a deep understanding of the following sub-sections included in this chapter. The elements analyzed and compared here concern the most relevant definitions used by each legislator, the general principles on the basis of which the EU and the US systems develop clinical trials norms, and the division of competences applicable in the context of clinical trials regulation and their enforcement.

#### *(a) Definitions*

The most important definition in the context of this analysis is that of clinical trials. Additionally, it is germane to provide a limited yet essential definition of other recurring terms often used by both the EU and the US legislator. Therefore, this section will analyze the definition – the nature and scope – of the following terms: (i) clinical trials (investigations, in the US framework) and (ii) sponsor, investigator, and subject.

##### *(i) Definition of Clinical Trials*

The first item that can be compared when looking at clinical trials regulation is the definition of clinical trials adopted by different legal systems.

At the EU level, the Clinical Trials Regulation provides for a two-tier test to define clinical trials to which the Regulation applies. The first tier focuses on the *aim of clinical studies*. There, clinical studies are defined as investigation in relation to humans intended

“(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; (b) to identify any adverse reactions to one or more medicinal products; *or* [emphasis added] (c) to study the absorption, distribution, metabolism and excretion of

one or more medicinal products; with the objective of certaining the safety and/or efficacy of those medicinal products.”<sup>273</sup>

The second tier focuses on the *conditions* to be fulfilled by any clinical study to be considered a *clinical trial*. A clinical trial is any clinical study (which passed the test established in the first tier) which additionally fulfills one of the following three conditions:

“(a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; *or* [emphasis added] (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.”<sup>274</sup>

With regard to the US, the CFR does not directly provide a definition of clinical trials. Instead, it focuses on the definition of “clinical investigation.” 21 US CFR 56.102 (c) reads as follows:

“[c]linical investigation means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505 (i) or 520 (g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.”<sup>275</sup>

It is worth noting that “the act” to which the provision refers is the Federal Food, Drug, and Cosmetic Act (FD&C Act) which is included in the US Code (USC) in Title 21.<sup>276</sup> Section 505 refers to new drugs and Section 505 (i) specifically refers to exemptions of drugs for research and discretionary and mandatory conditions.<sup>277</sup> Similarly, Section 520

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<sup>273</sup> Article 2.2 (1), EU CTR 536/2014.

<sup>274</sup> Article 2.2 (2), EU CTR 536/2014.

<sup>275</sup> 21 CFR 56.102 (c).

<sup>276</sup> 21 USC § 355. Note that a conversion table of the position of the provisions from the FD&C Act to the USC is available at: “FD&C Act Chapter V: Drugs and Devices.” *US Food and Drug Administration Home Page*,

[www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/FederalFoodDrugandCosmeticActFDCAAct/FDCAActChapterVDrugsandDevices/default.htm](http://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/FederalFoodDrugandCosmeticActFDCAAct/FDCAActChapterVDrugsandDevices/default.htm). In this contribution, provisions will be cited according to their position in the USC.

<sup>277</sup> 21 USC § 355 (i).

refers to general provisions respecting control of devices intended for human use, and Section 520 (g) specifically refers to exemptions for devices for investigational use.<sup>278</sup>

Three additional definitions of clinical trials can be observed and considered useful to better interpret and understand the choices of the EU and US legislators. First, the ICH defines clinical trials within its E6 Guideline on Good Clinical Practice. In particular, section 1.12 defines a clinical trial/study as

“[a]ny investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.”<sup>279</sup>

It is worth noting that as of October 2017, the guideline has already been implemented in the European framework<sup>280</sup> and its implementation in the US is still to be notified.<sup>281</sup>

Second, the definition provided by ClinicalTrials.gov, the US clinical trials registry. According to ClinicalTrials.gov, “[i]n a clinical trial, participants receive specific interventions according to the research plan or protocol created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants’ behavior (...).”<sup>282</sup>

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<sup>278</sup> 21 USCS § 360j (g).

<sup>279</sup> ICH Harmonised Guideline, *Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice*, E6(R2), Current Step 4 version dated 9 November 2016. The definition specifies also that “[t]he terms clinical trial and clinical study are synonymous.”

<sup>280</sup> Adopted by CHMP, 15 December 2016, issued as EMA/CHMP/ICH/135/1995 where CHMP stands for Committee for Human Medicinal Products cf. “ICH E6 (R2) Good clinical practice.” *European Medicines Agency - ICH E6 (R2) Good clinical practice*,

[www.ema.europa.eu/ema/index.jsp?curl=pages%2Fregulation%2Fgeneral%2Fgeneral\\_content\\_001251.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fregulation%2Fgeneral%2Fgeneral_content_001251.jsp).

<sup>281</sup> “Efficacy Guidelines.” *ICH*, [www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html](http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html).

<sup>282</sup> “Learn About Clinical Studies.” *ClinicalTrials.gov*, [clinicaltrials.gov/ct2/about-studies/learn#WhatIs](http://clinicaltrials.gov/ct2/about-studies/learn#WhatIs). The definition follows specifying that “[c]linical trials may compare a new medical approach to a standard one that is already available, to a placebo that contains no active ingredients, or to no intervention. Some clinical trials compare interventions that are already available to each other. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful, or no different than available alternatives (including no intervention). The investigators try to determine the safety and efficacy of the intervention by measuring certain outcomes in the participants. For example, investigators may give a drug or treatment to participants who have high blood pressure to see whether their blood pressure decreases.”

Third, the WHO – and, by extension, the International Clinical Trials Registry Platform – defines clinical trials as

“any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.”<sup>283</sup>

Comparing the two definitions introduced in each context, it is possible to draw some conclusions. First, all the observed definitions focus on clinical trials as studies *investigational in nature* and *involving human subjects*.

Second, the two main aspects in which the US approach and the EU one diverge – while however not reaching a contradiction – regard:

(i) The choice of the *object* to be defined. While the EU CTR distinguished between clinical studies and one of their sub-category, clinical trials – clashing with the ICH definition, according to which the two terms are synonyms –, the US CFR focuses on clinical investigations, without even touching upon the term “clinical trials.” While the US definition can be deemed to have the benefit of being more generic and therefore capable of covering more situations, the EU’s one has the benefit of setting a precisely applicable two-tier test.

(ii) The role of a study’s *aim* within the definition. While the EU CTR relies on the aim of a study to assess whether it falls within the “clinical study” definition provided in the first tier of the test. In the EU definition, the end-scope of commercialization is not prominent (assessing safety and efficacy of a treatment are). On the other hand, the US definition is completely focused on the aim of the clinical investigation; in fact, clinical trials fall within the US CFR basically any time they have the aim of testing a treatment that aims at obtaining the FDA approval for commercialization.

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<sup>283</sup> “Clinical trials.” *WHO*, World Health Organization, [www.who.int/topics/clinical\\_trials/en/](http://www.who.int/topics/clinical_trials/en/).

*(ii) Additional Definitions*

There are other three core concepts to be defined in the context of clinical trials regulation. They coincide with the three main stakeholders involved in clinical trials: sponsors, investigators, and human subjects.

Within the EU CTR, a *sponsor* is defined as “an individual, company, institution or organisation which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial.”<sup>284</sup> The US CFR reads as follows: “[sponsor] means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.”<sup>285</sup>

It can be noted how, on the one hand, the US set of definitions related to the concept of sponsors also provides for the figure of sponsor-investigator,<sup>286</sup> which is not envisaged within the EU legislation. On the other hand, the EU definition is an “open” one, which does not list for specific categories of sponsors while the US pre-identifies a list of subjects traditionally deemed to fall within the definition of sponsor.

An *investigator*, under the EU CTR, is “an individual responsible for the conduct of a clinical trial at a clinical trial site.”<sup>287</sup> The Regulation provides also for an additional definition for the concept of “principal investigator” being it “an investigator who is the responsible leader of a team of investigators who conduct a clinical trial at a clinical trial site.”<sup>288</sup> Under the US CFR investigator means “an individual who actually conducts a clinical investigation (*i.e.* under whose immediate direction the drug is administered or dispensed to a subject).”<sup>289</sup> As to the hierarchy between investigators, the CFR clarifies that “[i]n the event an investigation is conducted by a team of individuals, the investigator

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<sup>284</sup> Article 2.2 (14), EU CTR 536/2014.

<sup>285</sup> 21 CFR 312.3.

<sup>286</sup> See 21 CFR 312.3 according to which “Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.”

<sup>287</sup> Article 2.2 (15), EU CTR 536/2014.

<sup>288</sup> Article 2.2 (16), EU CTR 536/2014.

<sup>289</sup> 21 CFR 312.3.

is the responsible leader of the team. ‘Subinvestigator’ includes any other individual member of that team.”<sup>290</sup>

Therefore a slight yet potentially confusing difference between the approaches in the two legal systems can be observed: while in the US system, an investigator as a default option is the team leader (and team members are “subinvestigators”), in the EU system, an investigator as a default option is a team member (and the team leader is the “principal investigator”).

Finally, within the EU CTR, a *subject* is “an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.”<sup>291</sup> Interestingly, the EU CTR provides for corollary definitions of “minor”<sup>292</sup> and “incapacitated subject,”<sup>293</sup> unlike US clinical trials rules. In the US CFR, subject means “a human who participates in an investigation, either as a recipient of the investigational new drug or as a control.”<sup>294</sup> The CFR specifies that “[a] subject may be a healthy human or a patient with a disease.”<sup>295</sup>

Definitions in this field are extremely similar and, interestingly, they both introduce the option of participation in clinical trials with control groups. The EU definition is then expanded through reference to sub-categories of subjects, while the US one refers to the distinction between healthy and unhealthy patient.

### *(b) General Principles*

The EU CTR includes an article dedicated to stating a “general principle.” The aim of the article is to set the two basic conditions that must be cumulatively met for a clinical trial to be conducted. Those are: “(a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and (b) it is designed to generate reliable

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<sup>290</sup> 21 CFR 312.3.

<sup>291</sup> Article 2.2 (17), EU CTR 536/2014.

<sup>292</sup> Article 2.2 (18), EU CTR 536/2014 where minor “means a subject who is, according to the law of the Member State concerned, under the age of legal competence to give informed consent.”

<sup>293</sup> Article 2.2 (19), EU CTR 536/2014 where incapacitated subject “means a subject who is, for reasons other than the age of legal competence to give informed consent, incapable of giving informed consent according to the law of the Member State concerned.”

<sup>294</sup> 21 CFR 312.3.

<sup>295</sup> 21 CFR 312.3.

and robust data.”<sup>296</sup> The US CFR provides for a longer description of the principles behind the assessment of clinical trials appropriateness.<sup>297</sup> For now, it is worth noting that safety and rights of the subjects are the core principles that the FDA will protect in all phases of clinical trials and quality of the scientific evaluation (seen as a function of effectiveness and safety) are the primary objectives of the FDA’s action in phase 2 and 3 of clinical trials.<sup>298</sup> Hence, the protection of human subjects and the interest in scientific validity are common principles affirmed by both legislators.

*(c) Competences*

With regard to the delegation of competences which stands behind the implementation of the EU CTR and the US CFR (in the portions addressed in this contribution), it is worth noting that, within the EU system, competences on the matters addressed in the EU CTR are awarded to the supra-national level on the basis of the principle of subsidiarity and the principle of proportionality. Under the principle of subsidiarity, it is deemed appropriate for the EU to regulate clinical trials, as the goal of fully implementing the principles described above “cannot be sufficiently achieved by the Member States but can rather, by reason of its scale, be better achieved at Union level.”<sup>299</sup> Under the principle of proportionality, however, the EU CTR “does not go beyond what is necessary in order to achieve that objective.”<sup>300</sup>

Simultaneously, the federal competence to intervene in clinical trials regulation descends from the interstate commerce nature of clinical investigations – where the US use of “investigations,” as clarified above, corresponds to the European use of “trials”. Specifically, (i) in general, drugs must be the subject of an approved marketing application before being transported or distributed across state lines; (ii) before drugs obtain such approval, sponsors are likely to need to ship the investigational drug to clinical investigators in many states; (iii) therefore, sponsors willing to do so must seek an exemption from the legal requirement described under (i); (iv) to obtain such

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<sup>296</sup> Article 3, EU CTR 536/2014.

<sup>297</sup> 21 CFR 312.22.

<sup>298</sup> *Ibid.*

<sup>299</sup> Preamble (85), EU CTR 536/2014.

<sup>300</sup> *Ibid.*

exemption – which is awarded by the FDA – sponsors file an Investigational New Drug (IND) Application.<sup>301</sup>

## *(2) Application for Authorization*

The analysis of the provisions that regulate the application process for stakeholders interested in the conducting of clinical trials in the EU or US context encompasses considerations on two aspects: the procedural one and the one of content.

First, *procedure-wise*, sponsors willing to conduct clinical trials must file an application to competent authorities. At the US level, as clarified above, the competent authority to file an IND application is the FDA.<sup>302</sup> At the EU level, the identification of the competent authority/authorities is more complex. In fact, while applications to conduct clinical trials must be filed by sponsors through an EU portal,<sup>303</sup> the competence to assess whether the clinical trial applied for falls within the scope of the EU CTR and whether the application filed is complete in accordance with the EU CTR belongs to one EU Member State.<sup>304</sup> There are three main rules that can help sponsors to assess which Member State will be the competent one (i.e. the “reporting Member State): (i) it is generally up to the sponsor itself to propose one reporting Member State; (ii) if that Member is willing to be the reporting one or if the clinical trial involves only one Member State, that one shall be the reporting Member State; (iii) if more Member States are concerned with a clinical trial and there is no agreement among the Member States concerned as of which one should serve as reporting Member State, the proposed reporting Member State shall be the reporting one.<sup>305</sup>

Second, *content-wise*, applications submitted within the EU context and the US one present similar elements. The two legislators often use different terms to define such elements and often require applicants to provide the necessary contents under different

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<sup>301</sup> Center for Drug Evaluation and Research. “Investigational New Drug (IND) Application.” *US Food and Drug Administration Home Page*, Center for Drug Evaluation and Research, [www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm).

<sup>302</sup> See e.g. 21CFR 312.20 which reads as follows: “[a] sponsor shall submit an IND to FDA [emphasis added] if the sponsor intends to conduct a clinical investigation (...)”

<sup>303</sup> Article 5 (1) and Article 80, EU CTR 536/2014.

<sup>304</sup> Article 5 (3), EU CTR 536/2014.

<sup>305</sup> Article 5 (1), EU CTR 536/2014.

sections of their applications. However, five basic sections of the applications required in the two systems will be taken into consideration in this analysis. They are the following: (a) cover letter/sheet, introductory information, and application forms; (b) protocols; (c) the investigator's brochure; (d) chemistry, manufacturing, and control information; and (e) subject information, the informed consent form, and the informed consent procedure.

*(a) Cover Letter/Sheet, Introductory Information, and Application Forms*

Under the EU CTR, the letter, amongst other elements, should specify: the EU trial number and the universal trial number,<sup>306</sup> whether the clinical trial in question is considered to be a low-intervention clinical trial, whether the trial is expected to obtain informed consent from participants through simplified means.<sup>307</sup>

In this context, it is important to clarify that a “low-intervention clinical trial” within EU legislation means a clinical trial which cumulatively meets the following requirements:

“(a) the investigational medicinal products, excluding placebos, are authorised; (b) according to the protocol of the clinical trial, (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.”<sup>308</sup>

Despite the fact that the US CFR does not rely on the same concept of “low-intervention clinical trial,” it is worth noting that some of the cases in which sponsors are exempted from the duty to file an IND application are similar to those listed under the “low-intervention clinical trial” category in the EU CTR. In particular, under the US CFR exceptions apply when: a clinical investigation involves the use of a placebo but does not

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<sup>306</sup> Furthermore, in the case of a resubmission, “the cover letter shall specify the EU trial number for the previous clinical trial application, highlight the changes as compared to the previous submission and, if applicable, specify how any unresolved issues in the first submission have been addressed.” Annex I.B.12, EU CTR 536/2014. Note that applicants are required to submit a clinical trial number also under US legislation, certifying that the study is registered in the national database of clinical trials through FDA Form 3674.

<sup>307</sup> Annex I.B, EU CTR 536/2014.

<sup>308</sup> Article 2 (3), EU CTR 536/2014.

otherwise require the submission of an IND; the clinical investigation regards a drug product that is lawfully marketed in the US, when certain conditions apply regarding no prospective change of labelling or advertising; and no significant increase of the risk is entailed.<sup>309</sup> In this sense, the exceptions identified in the US CFR and those that define a low-intervention clinical trial in the EU CTR are extremely similar. However, an important caveat should be noted: while the exceptions listed in the US CFR are technically exempted from the duty to file an IND application, the trials that meet the low-intervention standard in the EU are not exempted from the duty to file an application but are “merely” subjected to “less stringent rules.”<sup>310</sup>

The US equivalent of the EU cover letter is the “Cover sheet (Form FDA-1571).” The latter is expected to include the following elements: the identification of the sponsor, or the phases of the clinical trial to be conducted, a commitment to await for the outcome of the IND application process, a commitment that an Institutional Review Board (IRB) will be responsible for the review of the study, the identification of monitoring subjects and of the contract research organization (CRO) if one is used.<sup>311</sup>

Preliminarily, two observations can be made. First, the US CFR – unlike the EU CTR – already addresses on its cover sheet the issue of applicants based outside the US. In fact, the US CFR specifies that if the applicant resides outside the US, the IND must be countersigned by an agent who resides or maintains a place of business within the US.<sup>312</sup>

Second, sponsors that file their application in the EU are not required to provide information regarding ethical review and monitoring in the cover letter, while applicants in the US are required to do so on the cover sheet. This aspect, however, merely has superficial value, as applicants in the EU are bound to address such issue in the EU application form in any event, while the latter must be submitted in addition to the cover letter. Currently the form is a 15 page document, which requires sponsors to provide some basic information and to check some boxes to describe the trial under standard

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<sup>309</sup> 21 CFR 312.2(b)(1).

<sup>310</sup> See Preamble(11), EU CTR 536/2014 which reads as follows “[t]hose clinical trials should be subject to less stringent rules, as regards monitoring, requirements for the contents of the master file and traceability of investigational medicinal products. In order to ensure subject safety they should however be subject to the same application procedure as any other clinical trial.”

<sup>311</sup> 21 CFR 312.23(a)(1).

<sup>312</sup> 21 CFR 312.23(a)(1)(ix).

categories e.g. information useful to identify the sponsor and its legal representative, the sponsor's status, the status of the products to be used in the clinical trial and its characteristics, information on the use of placebo, general information on the scope and the design of the trial, as well as on the targeted participants, prospective investigators, and ethical review authorities.<sup>313</sup> On the other hand, applicants in the US must accompany the cover letter with a bundle of introductory information, which is not expected under the EU CTR. The US table of "introductory statement and general investigational plan" includes – *inter alia* – information pertaining to the following elements: a brief introductory statement giving the name of the drug, the broad objectives and planned duration of the trial as well as other elements; a brief summary of previous human experience with the drug and – interestingly – "to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s);"<sup>314</sup> and information regarding e.g. risks of particular severity anticipated on the basis of the toxicological data in animals.<sup>315</sup> Therefore, while there seems to be a partial overlap in the information expected to be provided by applicants in the EU cover letter and the US cover sheet, it can be noted how applicants in the EU are also required to fill the EU application form, and applicants in the US are also required to provide general introductory information (which touches already upon the matter of products already tested abroad).

*(b) Protocols*

Annex I.D to the EU CTR describes the content of the clinical trial protocol to be included in the application. 11 sub-provisions regulate the content of the protocol and one of them (Annex I.D.17) lists 38 elements that represent the minimum content of the protocol. Given how extensive the norms are, this contribution will refrain from listing all of them. Nevertheless, it is useful to highlight how the elements expected to be addressed in the

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<sup>313</sup> A copy of the form – in a 2009 version – is available in "EudraLex - Volume 10 - Clinical trials guidelines - Public Health - European Commission." *Public Health*, 10 Sept. 2017, [ec.europa.eu/health/documents/eudralex/vol-10\\_en](http://ec.europa.eu/health/documents/eudralex/vol-10_en).

<sup>314</sup> Including information regarding the following: "[i]f the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal." 21 CFR 312.23(a)(3)(iii).

<sup>315</sup> 21 CFR 312.23(a)(3).

protocol are “the objective, design, methodology, statistical considerations, purpose and organisation of the clinical trial.”<sup>316</sup> As a result of this, protocols include details about design and safety procedures, lists of the products to be used and of the scientific findings that support the organization of the clinical trial, a description of the criteria to be used to select participants and of the monitoring procedures, and a description of the risk management strategies to be implemented especially in the case of adverse events.<sup>317</sup>

Similarly, the US CFR requires applicants to file a protocol with technical information presented. The requirements set for in the US CFR are different than the EU ones in two ways. First, the list provided for in the US CFR is more concise. Unlike the EU rules, e.g. it does not require sponsors to address the issue of procedures to be implemented in case of adverse effects. Second, unlike the EU CTR, it requires applicants to include the name and address of each reviewing IRB.<sup>318</sup> Third, while EU rules provide for a single set of requirements for protocols, independently from the phase involved in each clinical trials, US rules provide for a distinction on the basis of phases.<sup>319</sup> Fourth, US requirements included in the content of the protocol the identification of investigators.<sup>320</sup> This is not required within EU protocols, however, applicants in the EU must nevertheless provide such information in a different section of the application named “suitability of the investigator.” This section aims at identifying “the planned clinical trial sites, the name and position of the principal investigators and the planned number of subjects at the sites.”<sup>321</sup> In the application, the qualification of the investigators must be established and potential conflicts of interest must be identified.<sup>322</sup> Additionally, information must be provided regarding the suitability of the facilities,<sup>323</sup> proof of insurance cover of indemnification,<sup>324</sup> a description of the financial agreements behind

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<sup>316</sup> Annex I.D.14, EU CTR 536/2014.

<sup>317</sup> Annex I.D, EU CTR 536/2014.

<sup>318</sup> 21 CFR 312.23 (a)(6)(iii)(b).

<sup>319</sup> See 21 CFR 312.23 (a)(6)(i) which reads as follows: “protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies.”

<sup>320</sup> 21 CFR 312.23 (a)(6)(iii)(b).

<sup>321</sup> Annex I.M.64, EU CTR 536/2014. As of the sites, they must be described also under the US FCR, in particular through the submission of FDA Form 1572.

<sup>322</sup> Annex I.M.65 and I.M.66, EU CTR 536/2014.

<sup>323</sup> Annex I.N, EU CTR 536/2014.

<sup>324</sup> Annex I.O, EU CTR 536/2014.

the conduct of the clinical trial,<sup>325</sup> proof of payment of the fee (if applicable),<sup>326</sup> and proof that data will be processed in accordance with EU law on data protection i.e. Directive 95/46EEC.<sup>327</sup>

*(c) Investigator's Brochure*

The document has the purpose of reaching prospective investigators, later in the process. Therefore, its aim is to provide them with the information necessary to foster their understanding and compliance with the clinical trial, if approved.<sup>328</sup> The expected content of the document is similar under the EU CTR and the US CFR. However, two differences can be noted. First, under the US CFR the IB must include a description of “possible risks and side effects” of the treatment that is tested;<sup>329</sup> the IB described in the EU CTR, instead, refers to safety monitoring procedures and risk-benefit assessment but not explicitly to risks and side effects. Second, under the EU CTR the information provided in the IB shall be presented in a “non-promotional form”<sup>330</sup> and a similar caveat about the style of the IB is not included in US norms.

*(d) Chemistry, Manufacturing, and Control Information*

Under the EU CTR, sponsors are required to submit an investigational medicinal product dossier (IMPD). By definition, the IMPD aims at giving information on “the quality of any investigational medicinal product, the manufacture and control of the investigational medicinal product, and data from non-clinical studies and from its clinical use.”<sup>331</sup> IMPD rules are divided into three sub-sections that regard data relating to the investigational

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<sup>325</sup> Annex I.P, EU CTR 536/2014.

<sup>326</sup> Annex I.Q, EU CTR 536/2014.

<sup>327</sup> Annex I.R, EU CTR 536/2014.

<sup>328</sup> See Annex I.E.26, EU CTR 536/2014 – where IB stands for investigator’s brochure – which reads as follows: “[t]he purpose of the IB is to provide the investigators and others involved in the clinical trial with information to facilitate their understanding of the rationale for, and their compliance with, key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures.

<sup>329</sup> 21 CFR 312.23 (a)(5)(v) see also “[s]uch information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means”. 21 CFR 312.55 (b).

<sup>330</sup> Annex I.E.27, EU CTR 536/2014.

<sup>331</sup> Annex I.G.36, EU CTR 536/2014 note also that following Annex I.H, the IMPD requirements apply also to auxiliary medicinal products.

medicinal product,<sup>332</sup> simplified IMPD by referring to other documentation,<sup>333</sup> and IMPD in cases of placebo.<sup>334</sup> In the context of this contribution, it is interesting to note that the section of the EU CTR regarding the IMPD does not solely state EU standards but in more than one occasion refers to ICH standards to provide applicants with examples. This happens, for example, in the context of provisions on quality data,<sup>335</sup> non-clinical pharmacology and toxicology data,<sup>336</sup> and data from previous clinical trials and human experience.<sup>337</sup> Additionally to the IMPD, applicants may submit an auxiliary medicinal product dossier, a scientific advice and pediatric investigation plan (PIP), and the content of the labeling of the investigational medicinal product, and recruitment arrangements.<sup>338</sup> The latter section, in particular, includes copies of the advertising material to be used in case of recruitment through advertisement.<sup>339</sup> Furthermore, applicants in the EU are required to file any documentation relating to compliance with good manufacturing practice (GMP) for the investigational medicinal product.<sup>340</sup> Two very important provisions can be noted in this context because they represent a bridge between the EU context and potential connections with global clinical trials. First, the documentation should not be submitted “where the investigational medicinal product is authorised and is not modified.”<sup>341</sup> Interestingly, this exception applies, *whether or not* the product is manufactured in the EU.<sup>342</sup> Second, particular conditions are envisaged for products that

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<sup>332</sup> Annex I.G.37-49, EU CTR 536/2014.

<sup>333</sup> Annex I.G.50-53, EU CTR 536/2014.

<sup>334</sup> Annex I.G.54, EU CTR 536/2014.

<sup>335</sup> Annex I.G.40, EU CTR 536/2014 which reads as follows: “[q]uality data shall be submitted in a logical structure such as that of Module 3 of the ICH Common Technical Document format.” Cf. “The CTD triangle and M4: The Common Technical Document.” *ICH*, [www.ich.org/products/ctd.html](http://www.ich.org/products/ctd.html).

<sup>336</sup> Annex I.G.42, EU CTR 536/2014 which reads as follows: “[n]on-clinical pharmacology and toxicology data shall be submitted in a logical structure, such as that of Module 4 of the ICH Common Technical Document format.”

<sup>337</sup> Annex I.G.46, EU CTR 536/2014 which reads as follows: “[d]ata from previous clinical trials and human experience shall be submitted in a logical structure, such as that of Module 5 of the ICH Common Technical Document format.”

<sup>338</sup> Annex I.H-K, EU CTR 536/2014.

<sup>339</sup> Annex I.K.60, EU CTR 536/2014.

<sup>340</sup> Annex I.F, EU CTR 536/2014 note also that following Annex I.H, the IMPD requirements apply also to auxiliary medicinal products.

<sup>341</sup> Annex I.F.32, EU CTR 536/2014.

<sup>342</sup> *Ibid.*

are not authorized within the EU but have a marketing authorization from a third country that is party to the ICH.<sup>343</sup>

Similarly, in the US context, applicants are required to provide information regarding the composition, manufacture, and control of the drug substance and the drug product as well as pharmacology and toxicology information.<sup>344</sup> While the list of requirements included in the US CFR is less detailed than that included in the EU CTR, it is important to note that in the US framework, the case of products already tested and/or commercialized in other countries is also foreseen. In particular, US legislation provides that (a) “if the investigational drug has been investigated or marketed previously, either in the US or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation’s rationale”<sup>345</sup> and (b) “if the drug has been marketed outside the US, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.”<sup>346</sup> In this sense, provisions regarding products tested or commercialized abroad seem more stringent in the US context, and in any event, the amount of information pertaining to such products that applicants are required to disclose is greater under US standards than under EU standards.

*(e) Subject Information, Informed Consent Form, and Informed Consent Procedure*

Under the EU CTR, applicants must submit information regarding informed consent forms,<sup>347</sup> procedures in place to protect vulnerable subjects (e.g. incapacitated subjects),<sup>348</sup> involving witnesses,<sup>349</sup> in place in case of emergency situations,<sup>350</sup> or for cases in which simplified means to obtain informed consent are sought.<sup>351</sup> All of these elements fall within a specific section of the EU application. On the contrary, US norms do not provide for a specific portion of the application to focus on human subjects’

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<sup>343</sup> Cf. Annex I.F.33-35 and Article 61, EU CTR 536/2014.

<sup>344</sup> 21 CFR 312.23 (a)(7)(i) and 21 CFR 312.23 (a)(8).

<sup>345</sup> 21 CFR 312.23 (b)(iii)(9)(i).

<sup>346</sup> 21 CFR 312.23 (b)(iii)(9)(iii).

<sup>347</sup> Annex I.I.61, EU CTR 536/2014.

<sup>348</sup> Annex I.I.62, EU CTR 536/2014.

<sup>349</sup> *Ibid.*

<sup>350</sup> *Ibid.*

<sup>351</sup> *Ibid.*

guarantees and informed consent. Instead, applicants in the US are expected to address the criteria for participants' selection and protection within the protocol.<sup>352</sup> As for their duty to address informed consent-related issues, despite the fact that other portions of the CFR (outside the context of IND applications) are dedicated to the matter, the only reference included in 21 CFR 312.23 regards the need of pre-identification of exception from informed consent.<sup>353</sup>

### *(3) Assessment of the Application*

Assessment procedures can be compared on the basis of different elements. The following paragraphs in this contribution will deal with four specific aspects: the timing of the assessment process, the bodies entrusted with the assessment, the criteria to be used in the assessment process, and the possible outcomes of the assessment.

#### *(a) Timing of the Assessment Process*

With regard to the timing of the assessment process, the EU CTR provides that sponsors and the concerned Member States must be notified by the reporting Member State of the assessment report through the EU portal within 45 days from the validation date of the application. For the purpose of the regulation, the validation date does not necessarily coincide with the date in which the application was filed. Rather, the 45-day term starts running from the day in which a sponsor was notified by the reporting Member State that the application submitted was (or was not) found to fall within the scope of the EU CTR and was (was not) deemed to be complete.<sup>354</sup> The notification regarding the pertinence and completeness of the application, in any event, must take place within 10 days since the application submission.<sup>355</sup> Hence, sponsors will receive a response regarding the admission or rejection of their clinical trials in the EU within 55 days from the filing of the application.

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<sup>352</sup> Cf. 21 CFR 312.23 (a)(6)(iii)(c).

<sup>353</sup> 21 CFR 312.23 (f).

<sup>354</sup> Article 5 (6), EU CTR 536/2014.

<sup>355</sup> Article 5 (3), EU CTR 536/2014.

Within the US framework, applications are technically processed by the Center for Drug Evaluation and Research, as part of the FDA.<sup>356</sup> Following the submission of the application, the will enter into force after 30 days, unless the FDA notifies the sponsor that a clinical hold is applied.<sup>357</sup> A clinical hold is an order issued “to delay a proposed clinical investigation or to suspend an ongoing investigation.”<sup>358</sup> If a clinical hold is put into place within the 30 days term, the sponsor will receive a written explanation of the hold within 30 days after the imposition of the hold.<sup>359</sup> (b) Bodies Entrusted with the Assessment

With regard to the bodies entrusted with the assessment, in the EU framework, the ultimate decision regarding the authorization of clinical trials is left to the Member States. Member States determine autonomously which bodies to involve in the assessment as a matter of internal organization.<sup>360</sup> The EU CTR, however, refers to such bodies as “ethics committees” and specifies some core requirements: the involvement of at least one layperson, the involvement of qualified and experienced subjects, the involvement of specifically qualifies subjects in specific circumstances,<sup>361</sup> the lack of conflicts of interest between the members of the committees and any of the stakeholders involved in the clinical trials examined.<sup>362</sup> In the US, while the ultimate decision regarding any IND application lies with the FDA, the assessment of the clinical trials is traditionally assigned to Institutional Review Board (IRB). Under the US CFR, clinical trials cannot initiate unless they have been reviewed and approved by an IRB.<sup>363</sup> While the bodies entrusted

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<sup>356</sup> Center for Drug Evaluation and Research. “About the Center for Drug Evaluation and Research.” *U S Food and Drug Administration Home Page*, Center for Drug Evaluation and Research, [www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm).

<sup>357</sup> 21 CFR 312.40(b)(1). See also “Investigational New Drug Application (IND) Process Overview.” *Investigational New Drug Application (IND) Process Overview | Clinical Trials | Health Care Professionals | Dartmouth-Hitchcock*, [med.dartmouth-hitchcock.org/clinical\\_trials/ind\\_process\\_overview.html](http://med.dartmouth-hitchcock.org/clinical_trials/ind_process_overview.html).

<sup>358</sup> 21 CFR 312.42 (a).

<sup>359</sup> 21 CFR 312.42 (d).

<sup>360</sup> Preamble (18), EU CTR 536/2014.

<sup>361</sup> In addition, “[s]pecific expertise should be considered when assessing clinical trials involving subjects in emergency situations, minors, incapacitated subjects, pregnant and breastfeeding women and, where appropriate, other identified specific population groups, such as elderly people or people suffering from rare and ultra rare diseases.” Preamble (19), EU CTR 536/2014.

<sup>362</sup> Preamble (18) and Article 9, EU CTR 536/2014.

<sup>363</sup> 21 CFR 56.103 (a). The requirement does not apply to some exceptional cases; in particular, trials commenced before July 27, 1981, emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days, some taste and food quality evaluations and consumer

with the assessment under the EU CTR are not necessarily the same that will keep reviewing over time the clinical trial that they have approved, clinical trials in the US remain subject to continuing review by an IRB during the whole length of the trial.<sup>364</sup> In practical terms, IRBs are bodies – both private and public in nature –, which have undergone a registration process through the FDA.<sup>365</sup> The US CFR provides with some details about the composition of IRBs in a way that is more detailed than the EU CTR. In particular, while – similarly to ethics committees in the EU framework –, IRBs’ members are expected to be selected on the basis of “experience and expertise,” if necessary considering the involvement of specifically qualified subjects in specific circumstances,<sup>366</sup> and are expected to have no conflict of interest with the projects assessed,<sup>367</sup> specific considerations apply to IRBs which are not to be found in the EU framework. For example, the US FCR provides that IRBs must: be composed of at least 5 members and on the basis of diversity-considerations;<sup>368</sup> ensure diversity of gender in its composition; not consist entirely of members of one single profession; and collectively possess the expertise to assess not only the scientific validity of a project but also its organizational feasibility and compliance with the law.<sup>369</sup> In the US CFR, there is not provision similar to Article 6 of the EU CTR requiring laypersons to be involved in the assessment process; however, the US CFR provides that “[e]ach IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.”<sup>370</sup>

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acceptance studies, and in cases in which the FDA decides to waive the IRB requirement. See 21 CFR 56.104 and 56.105.

<sup>364</sup> Cf. 21 CFR 56.103 (a).

<sup>365</sup> The registration requirements are listed in 21 CFR 56.106.

<sup>366</sup> See 21 CFR 56.107 which reads as follows “[i]f an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.”

<sup>367</sup> 21 CFR 56.107.

<sup>368</sup> See 21 CFR 56.107 (a) which reads as follows: “including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes (...).”

<sup>369</sup> 21 CFR 56.107 and, specifically, see section (a) which reads as follows: “[i]n addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.”

<sup>370</sup> 21 CFR 56.107 (d).

*(b) Criteria to be Used in the Assessment Process*

With regard to the criteria to be used in the assessment process, it is important to note that in the EU framework the Member States are provided with a single set of criteria to be used in the assessment. Differently, criteria relevant in the US framework can be found in two sets of provisions: those regarding the IRB criteria for approval of research and those regarding the grounds for the imposition of a clinical hold by the FDA.<sup>371</sup>

In the EU framework, the assessment is conducted on the basis of the “anticipated therapeutic and public health benefits” and the “risks and inconveniences for the subjects.”<sup>372</sup> Furthermore, compliance with the requirements concerning the manufacturing of the products, labeling requirements, and completeness and adequateness of the IB is assessed.<sup>373</sup> With regard to specific concerns for the protection of subjects, assessment criteria focus on compliance with informed consent requirements, rewarding/compensation policies, suitability of sites and investigators, and data protection requirements.<sup>374</sup> EU norms provide also for an additional set of provisions that belong to the context of assessment-criteria and do not strictly regard the approval process for clinical trials but rather the division of competences between different Member States involved in the process.<sup>375</sup>

In the US framework, the concerns assessed by IRBs are similar. In order to approve research projects, IRBs must consider the following issues: the risks for subjects, with one of the concerns being the avoidance of unnecessary risks;<sup>376</sup> the risks-benefits balance, where, however, two elements are not to be considered: “risks and benefits of therapies that subjects would receive even if not participating in the research” and “the possible effects of the research on public policy;”<sup>377</sup> the equitableness of subjects’ selection;<sup>378</sup> the quality of informed consent procedures to be implemented;<sup>379</sup> the

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<sup>371</sup> See respectively 21 CFR 56.11 and 21 CFR 312.42.

<sup>372</sup> Article 6.1(b), EU CTR 536/2014.

<sup>373</sup> Article 6.1(c)-(e), EU CTR 536/2014.

<sup>374</sup> Article 7.1, EU CTR 536/2014.

<sup>375</sup> E.g. Article 6.5-8, EU CTR 536/2014.

<sup>376</sup> 21 CFR 56.111 (a)(1).

<sup>377</sup> 21 CFR 56.111 (a)(2).

<sup>378</sup> 21 CFR 56.111 (a)(3).

<sup>379</sup> 21 CFR 56.111 (a)(4)-(5).

policies implemented for data protection and privacy concerns.<sup>380</sup> It is interesting to note that both legal systems provide for caveats to be considered in the case of clinical trials involving vulnerable subjects. However, the identification of vulnerable subjects, as well as the identification of the concerns related to their participation in clinical trials is more extensive in the case of US legislation. In fact, under the EU framework, Article 10 CTR prescribes that specific considerations shall be given to the assessment of applications for clinical trials involving minors, incapacitated subjects, pregnant or breastfeeding women, and emergency trials.<sup>381</sup> However, the EU CFR does not specifically identify the major concerns to be considered in the context of research involving vulnerable subjects. On the other hand, the US CFR identifies a longer list of subjects: “children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.”<sup>382</sup> It also identifies the specific concern behind the need to protect those subjects as being vulnerable to coercion and undue influence.<sup>383</sup> Aside from the IRBs’ assessment, the FDA, in deciding whether to impose a clinical hold, will take into consideration the following elements: unreasonable and significant risk of illness or injury for participants,<sup>384</sup> unqualified clinical investigators, misleading, erroneous, or materially incomplete IB, lack of information in the IND application, and in the case of projects “not designed to be adequate and well-controlled.”<sup>385</sup> Interestingly, while the elements listed so far are to be considered for Phase 1 studies; for Phase 2 or 3 studies, an additional ground for clinical holds is the deficient design of the study to meet

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<sup>380</sup> Note, however, that the US CFR adds a caveat in the case of data protection and privacy concerns that makes the assessment of the IBR more discretionary than for other elements. In fact, the wording of 21 CFR 56.111 (a)(6)-(7) sets the standard to “when appropriate.”

<sup>381</sup> Article 10, EU CTR 536/2014. in addition, the preamble refers to a concern for economically disadvantaged subjects but does not associate any prescription regarding an absolute need for their protection. See: “[i]n order to certify that informed consent is given freely, the investigator should take into account all relevant circumstances which might influence the decision of a potential subject to participate in a clinical trial, in particular whether the potential subject belongs to an economically or socially disadvantaged group or is in a situation of institutional or hierarchical dependency that could inappropriately influence her or his decision to participate.” Preamble (31), EU CTR 536/2014

<sup>382</sup> 21 CFR 56.111 (b).

<sup>383</sup> Ibid.

<sup>384</sup> A more specific concern regards “[t]he IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (i.e., affecting reproductive organs) or developmental toxicity (i.e., affecting potential offspring).” 21 CFR 312.42 (b)(v)

<sup>385</sup> 21 CFR 312.42 (b).

its objectives.<sup>386</sup> On the other hand, the EU CTR does not distinguish concerns on the basis of the phases that clinical trials are addressing.

*(c) Possible Outcomes of the Assessment*

Finally, with regard to the possible outcomes of the assessment, the US system maintains a two-tier process in which clinical trials applications are examined first by an IRB and then by the FDA. At the IRB-level, IRBs have the authority to “approve, require modifications in (to secure approval), or disapprove all research activities.”<sup>387</sup> At the FDA level, the agency has the power to approve a clinical trial application or to impose a clinical hold in order to delay the proposed investigation or suspend an ongoing one.<sup>388</sup> In the EU framework, the reporting Member State can conclude its assessment report finding that the clinical trial project is either acceptable under the EU CTR’s requirements, or acceptable but subject to compliance with specific conditions listed in the conclusion, or not acceptable under the EU CTR’s requirements.<sup>389</sup> Despite the lack of specific instructions given by the EU CTR to national ethics review boards, the EU CTR adds a further level of review that can be triggered in certain cases. This regards the situation in which a concerned Member State may disagree with the conclusions drawn by the reporting Member State. The only grounds on which objections may be raised by the concerned Member State are the following: when “participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned,” when its national law on the use of any specific type of human or animal cells or derived products, or considerations regarding subjects safety and data reliability and robustness.<sup>390</sup>

In conclusion, the approval protocols in the EU and the US framework present both several similarities and differences. On the one hand, the main similarities regard the timing of the assessment and the criteria to be used in the assessment. On the other hand, the main differences, concern three principal points. First, the structure of the assessment mechanism in terms of institutional bodies involved. In this context, the EU assessment

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<sup>386</sup> 21 CFR 312.42 (b)(v)(C)(2)(ii).

<sup>387</sup> 21 CFR 56.109 (a).

<sup>388</sup> 21 CFR 312.42 (a).

<sup>389</sup> Article 6.3 (a)-(c), EU CTR 536/2014.

<sup>390</sup> Article 8.2(a)-(c), EU CTR 536/2014.

is principally conducted by national review boards instituted in the Member States but under the instructions included in the EU CTR and with the possibility for concerned Member States to object the assessment's outcome. In the US, the assessment has a two-tier structure in which first IRBs are involved and then the FDA is involved. The second point relates to the protection of vulnerable subjects – in which case, the US CFR provides for a longer list of subjects and specifies that the main concern for clinical trials that involve them regards coercion and undue influence, while the EU CTR provides for a shorter list and no identification of specific concerns to be taken into consideration. The third point concerns the possible outcome of the assessment process, where, in the US system, sponsors may be granted an exception (that *de facto* will allow them to conduct the clinical trial) or be subjected to a clinical hold, while in the EU system sponsors may receive a full approval, a conditional one, or a rejection of their application.

#### *(4) Specific Concerns*

There are two additional issues that this comparative analysis takes into consideration. Both regard aspects of clinical trials design and application, which are intrinsically connected with concerns for the protection of human subjects: rules applicable to the use of placebo in clinical trials and rules applicable to the design and obtainment of informed consent. They will be analyzed in this sub-section, as they represent concerns that are particularly relevant in terms of the protection of the human subjects who take part in clinical trials. One additional issue regards the life of clinical trials following their approval and specifically the control procedures to which they are subjected and will be addressed in the following sub-section.

##### *(a) Use of Placebo in Clinical Trials*

As noted earlier, the use of placebo trials is often controversial.<sup>391</sup> In the EU CTR context, repeated reference to the use of placebo is made. The first regards the definition within which placebos fall, which is the “investigational medicinal product” one.<sup>392</sup> The second one regards the simplified IMPD application within which, if the investigational medical

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<sup>391</sup> Cf. e.g. Gupta and Verma, *op. cit.*

<sup>392</sup> Annex I (54), EU CTR 536/2014.

product is a placebo, applicants are only required to provide quality data.<sup>393</sup> No reference is made within the EU CTR to the need for the use of placebo-controlled trials to be limited as much as possible. However, good clinical practice standards – to which the same EU CTR refers – as well as the European Medicines Agency have over time clarified the scope of the use of placebo in clinical trials conducted in the EU. In particular, their considerations suggest that the current standard in the EU territory is based on two elements. First, the fact that placebo-controlled trials are not *per se* prohibited, even in areas in which proven prophylactic and therapeutic methods exist.<sup>394</sup> Second, ethical considerations should *limit* the use of placebo-controlled trials. Those considerations include (i) concerns for the risk of irreversible harm to the subjects, (ii) the need for the obtainment of an adequate informed consent, (iii) the right of subjects to withdraw from a clinical trial, but still receive conventional treatment, and (iv) the need to apply identical standards to trials conducted outside the EU territory.<sup>395</sup>

In the US context, similarly, there is no prohibition of the use of placebo *per se*. In fact, placebo-controlled trials are one of the five categories identified by the FDA in response to effectiveness concerns (the five categories being placebo concurrent control, dose-response concurrent control, no-treatment concurrent control, active treatment concurrent control, and historical control).<sup>396</sup> However, both under applicable legal standards and common clinical practice, reliance upon placebo-controlled trials principally arises in the context of add-on treatments to standard therapy or in the case of patients refractory to standard treatment.<sup>397</sup> Add-on treatments, in particular, are those in which “when a placebo is used, standard care, if any, would be given to all subjects, with subjects randomized to receive, in addition, the test treatment or a placebo.”<sup>398</sup> Despite the fact that they represent traditional usages of placebo in clinical trials, under

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<sup>393</sup> Furthermore, “[n]o additional documentation is required if the placebo has the same composition as the tested investigational medicinal product (with the exception of the active substance), is manufactured by the same manufacturer, and is not sterile.” Article 2.2(6), EU CTR 536/2014.

<sup>394</sup> European Agency for the Evaluation of Medicinal Products, Pre-authorisation Evaluation of Medicines for Human Use (London, 28 June 2001) EMEA/17424/01.

<sup>395</sup> *Ibid.*

<sup>396</sup> 61 FR 51498 and Office of the Commissioner. “Search for FDA Guidance Documents - Drug Study Designs - Information Sheet.” *US Food and Drug Administration Home Page*, Office of the Commissioner, [www.fda.gov/RegulatoryInformation/Guidances/ucm126501.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm126501.htm).

<sup>397</sup> FDA, “Placebo-controlled Trials: Are They Ethical? Are They Necessary?” Presentation available at <https://www.fda.gov/ohrms/dockets/ac/00/slides/3641s1d.ppt>

<sup>398</sup> 61 FR 51498.

US legislation they are not necessarily the only cases in which placebo may be used. In fact, the US CFR provides that “[a] placebo-controlled study *may* [emphasis added] include additional treatment groups, such as an active treatment control or a dose-comparison control, and usually includes randomization and blinding of patients or investigators, or both.”<sup>399</sup> Hence, the use of placebo – even when a better available standard of care exists – is not openly prohibited by the FDA but in normal circumstances, the agency expects clinical trials to be placebo-controlled mainly in the context of add-on treatments. To conclude, neither in the EU nor in the US context is reliance on placebo-controlled clinical trials prohibited *per se*, but ethical and practical considerations limit sponsors’ recourse to it where alternative designs are available.<sup>400</sup>

### *(b) Informed Consent Regulation*

Informed consent rules to be applied in the context of clinical trials and set in the EU and the US frameworks are similar yet not identical. This section will compare the two sets of provisions and identify elements that are unique to each legal system.

Under the EU CTR, the first caveat regarding informed consent is included in the preamble. It specifies that Member States should cooperate in the assessment of any clinical trial authorization, but that aspects of intrinsically national nature (e.g. informed consent) are not included in such duty to cooperate.<sup>401</sup> Despite the identification of informed consent procedures as intrinsically national in nature, the EU CTR addresses the issue of informed consent in several ways. First, it identifies informed consent as one of the essential requirements supporting the legality of clinical trials. It does so both referring to the Charter of Fundamental Rights of the EU and the value of human dignity, and listing the technical elements necessary to approve a clinical trial.<sup>402</sup> Similarly,

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<sup>399</sup> 21 CFR 314.126 (b)(2)(i).

<sup>400</sup> Cf. “Access Services to Enable Research.” *Placebo Controls – Are they Ethically Acceptable in a Clinical Trial?* | *CTSI Services for Researchers*, [accelerate.ucsf.edu/blogs/ethics/placebo-controls-%E2%80%93-are-they-ethically-acceptable-clinical-trial](https://accelerate.ucsf.edu/blogs/ethics/placebo-controls-%E2%80%93-are-they-ethically-acceptable-clinical-trial).

<sup>401</sup> Preamble (6), EU CTR 536/2014.

<sup>402</sup> See Preamble (27), EU CTR 536/2014: “Human dignity and the right to the integrity of the person are recognised in the Charter of Fundamental Rights of the European Union (the ‘Charter’). In particular, the Charter requires that any intervention in the field of biology and medicine cannot be performed without free and informed consent of the person concerned” and Article 28, EU CTR 536/2014: “A clinical trial may be conducted only where all of the following conditions are met: (...) the subjects, or where a subject is not able to give informed consent, his or her legally designated representative, have been informed in accordance with Article 29(2) to (6).”

informed consent is an essential element of clinical trials approval in the US framework.<sup>403</sup>

The EU CTR requires informed consent to be written, dated and signed by the professional conducting the informed consent interview and by the subject.<sup>404</sup> Furthermore, the subject must be given adequate time to consider her decision to take part in the research and must be given a copy of the document.<sup>405</sup> Similarly, under the US CFR, sufficient time must be given to the subject to consider her decision to participate,<sup>406</sup> the subject must receive a copy of the consent form,<sup>407</sup> and the date of the signature of the form must be entered.<sup>408</sup> It appears like the signatures explicitly relevant in the US context are those of the subject and his or her legal representative (if one is involved) and that – unlike in the EU system – no signature of an investigator is required. As to the availability of means alternative to written consent and language requirements, in the EU, audio or video recorders may be used when necessary but a witness must be present and interviews with any subject should take place “in a language which is easily understood by him or her.”<sup>409</sup> It is not clear whether the latter requirements refer to the use of technical language vs lay language, or the mother tongue of the participant (e.g. for immigrants). In the US context, reliance on has a different meaning to traditional written consent. Such a conclusion can be made in two situations: first, when use of a short form is allowed and the elements of informed consent are presented orally to the subject.<sup>410</sup> Alternative methods of obtaining informed consent (e.g. via telephone, email, and in general not in face-to-face circumstances) are constantly discussed and monitored by the FDA.<sup>411</sup> As of the language-concern, US legislation relies on the goal of

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<sup>403</sup> With the exclusion of some exceptions, “no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.” 21 CFR 50.20.

<sup>404</sup> Article 29.1, EU CTR 536/2014.

<sup>405</sup> *Ibid.* Note also that the prior interview must be conducted by a “member of the investigating team who is appropriately qualified according to the law of the Member State concerned.” Article 29.2(c), EU CTR 536/2014.

<sup>406</sup> 21 CFR 50.20.

<sup>407</sup> 21 CFR 50.27 (a).

<sup>408</sup> *Ibid.*

<sup>409</sup> Preamble (30), EU CTR 536/2014.

<sup>410</sup> 21 CFR 50.27 (b)(2).

<sup>411</sup> FDA, Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, 2014, at p. 17.

understandability without specifically referring to non-English speaking participants; however, FDA guidelines provide for instructions to be used in case of non-English speaking participants.<sup>412</sup>

As for the elements of informed consent, the EU CTR lists seven basic requirements. Informed consent should enable subjects to understand (i) “nature, objectives, benefits, implications, risks and inconveniences of the clinical trial,” (ii) their rights and guarantee, in particular in case of refusal to participate and withdrawal, (iii) the conditions of the clinical trial (e.g. expected duration), (iv) possible treatment alternatives, and (v) follow-up measures if the participation in the clinical trial is discontinued.<sup>413</sup> Furthermore, subjects must be provided with information regarding (vi) the applicable damage compensation and (vii) the EU trial number and information on the availability of results.<sup>414</sup> The goal of the first five elements is strictly tied to the need for participants to understand information pivotal to the formation of their free consent, while the last two elements regard more widely information that must be provided (without any specific focus on the need for subjects to understand it). The EU CTR provides also that informed consent procedures shall be kept “understandable to a layperson.”<sup>415</sup>

Similar elements can be found in the US CFR requirements, though the latter often appear to be more detailed. Under the US CFR, informed consent procedures are expected to include (a) a description of the clinical investigation – which encompasses a description of the procedures and their purposes, including practical information e.g. about the number of clinical visits expected.<sup>416</sup> This element is similar to the one identified under (i) and (iii) above. (b) A description of “any reasonably foreseeable risk or discomforts to the subjects.”<sup>417</sup> This statement is more precise than the one included under (i) above, as the threshold is clearly set by the foreseeability of risks in the US system,<sup>418</sup> while it

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<sup>412</sup> *Ibid.* at p. 30. Note, in any event, that individuals cannot be routinely excluded from participation because they do not understand English cf. 21 CFR 56.111 (a)(3).

<sup>413</sup> Article 29.2(a), EU CTR 536/2014.

<sup>414</sup> Article 29.2(d)-(e), EU CTR 536/2014.

<sup>415</sup> Article 29.2(b), EU CTR 536/2014.

<sup>416</sup> 21 CFR 50.25 (a)(1) and FDA, Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, 2014, at p. 7.

<sup>417</sup> 21 CFR 50.25 (a)(2).

<sup>418</sup> Except in certain situations in which a statement about unforeseeable risks may be included in informed consent forms under 21 CFR 50.25 (b)(1).

may entail both foreseeable and unforeseeable risks in the EU. (c) A description of the expected benefits,<sup>419</sup> as under (i) above. (d) A disclosure of appropriate alternative procedures,<sup>420</sup> as under (iv) above. It is worth noting that in addition to this, distinct from the EU CTR, the FDA recommends that subjects are also informed about the care that they would receive if they were to decide not to take part in the research<sup>421</sup> and about the effect of participation in one trial on eligibility to participate in others.<sup>422</sup> (e) A statement about the confidentiality policy to be applied to medical records pertinent to the clinical trial,<sup>423</sup> which appears to be different than the rule on availability of clinical trial results under the EU CTR described in (vii) above. (f) An explanation of the compensation available in the case of injuries,<sup>424</sup> as under (vi) above. A difference exists between the two legal standards in this context: while under the EU CTR Member States *shall* ensure for damage compensation mechanisms,<sup>425</sup> in the US context it is possible to organize clinical trials in which no damage compensation is available e.g. due to hospital policies.<sup>426</sup> (g) The contacts of competent subjects that may be reached to obtain clarifications regarding the clinical trial.<sup>427</sup> This element is not explicitly present in EU legislation. (h) A statement regarding the voluntariness of the participation and the possibility of withdrawal,<sup>428</sup> as in (ii) above. Differently than EU legislation (point (v) above), the fundamental elements identified in the US CFR do not include provisions on the involuntary termination of subjects' participation. Information regarding that case, in the US context, are to be included in informed consent documents only when appropriate.<sup>429</sup> Further information that can be presented in the US context (when appropriate) and that are not listed in the EU CTR concern: unforeseeable risks, additional costs to subjects,

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<sup>419</sup> 21 CFR 50.25 (a)(3).

<sup>420</sup> 21 CFR 50.25 (a)(4).

<sup>421</sup> 21 CFR 50.25 (a)(1) and FDA, *Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors*, 2014, at p. 7.

<sup>422</sup> *Ibid.*, at p. 10.

<sup>423</sup> 21 CFR 50.25 (a)(5).

<sup>424</sup> 21 CFR 50.25 (a)(6).

<sup>425</sup> Article 76, EU CTR 536/2014.

<sup>426</sup> In that case disclaimers *should* include statements about e.g. hospital policies in the informed consent documents. See FDA, *Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors*, 2014, at p. 11.

<sup>427</sup> 21 CFR 50.25 (a)(7).

<sup>428</sup> 21 CFR 50.25 (a)(8).

<sup>429</sup> 21 CFR 50.25 (b)(2).

consequences of withdrawal, significant new findings and the policy for their disclosure, and the number of subjects involved in clinical trial.<sup>430</sup>

There are two categories of particular circumstances in which standard norms prescribed for informed consent procedures do not entirely apply. They regard cases in which the threshold to obtain informed consent is lowered; and cases in which the threshold to obtain consent is heightened. They will be analyzed and compared in the following paragraphs.

*(i) Lowered Informed Consent Standards*

Both in the EU and the US systems, in certain circumstances, legislators allowed for informed consent to be obtained in ways that are procedurally less complex than in the standard case. The main case is the one of emergency participation in clinical trials.

First, under EU legislation, clinical trials in emergency situations result in the need to obtain informed consent “only” after the decision to include the subject in the trial “provided that this decision is taken at the time of the first intervention on the subject, in accordance with the protocol for that clinical trial” and that six conditions are met.<sup>431</sup> In the US context, the consequence of a finding of emergency situation renders unnecessary the obtaining of informed consent.<sup>432</sup> The finding is subject to several requirements and procedural steps.

Second, in the US context, the assessment of the presence of an emergency situation is left to the investigator *and* “a physician who is not otherwise participating in the clinical investigation.”<sup>433</sup> Furthermore, the documentation regarding the assessment of the emergency situation is then expected to be submitted to an IRB.<sup>434</sup> The EU CTR does not clarify which subjects are to be involved in the assessment of emergency situations.

Third, under the EU CTR, six conditions must be met for a clinical trial in an emergency situation to be allowed. They regard the existence of (1) sudden life-threatening or serious

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<sup>430</sup> 21 CFR 50.25 (b).

<sup>431</sup> Article 35, EU CTR 536/2014.

<sup>432</sup> 21 CFR 50.23.

<sup>433</sup> 21 CFR 50.23 (a). Also, following 21 CFR 50.23 (b), the opinion of the independent physician may be obtained *ex post* under certain circumstances, but within 5 days from the start of the trial on the patient.

<sup>434</sup> 21 CFR 50.23 (c).

condition that makes the subject incapable of giving informed consent; (2) scientific grounds which allow to expect measurable health-improvement for the subject; (3) impossibility to obtain informed consent from the subject's representative within the "therapeutic window;" (4) absence of known objections to participate previously expressed by the subject; (5) characteristics of the trial that make it possible only in emergency situations – it is not clear whether this requirement refers to the subjective situation of the participant or to the nature of the trial; (6) minimal risk and minimal burden for the subject, in comparison with the standard available treatment.<sup>435</sup> Under the US CFR, four conditions must exist: (1) life-threatening situation<sup>436</sup> – which differs from the EU standard to the extent that it must involve a life-threatening situation and not, in alternative, a "serious condition;" (2) impossibility to obtain informed consent from the subject's representative,<sup>437</sup> as under EU standards; (3) impossibility to obtain informed consent from the subject,<sup>438</sup> as under EU standards; (4) "no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject."<sup>439</sup> The last requirement refers directly to a comparison between available treatments and the one to be tested in terms of effectiveness, while the EU CTR only compares treatments in terms of risks and burden for subjects. An additional difference between the two tests lies in the lack of reference to possible previous objections of the subject in the US context.

Fourth, it is worth noting that the EU CTR describes the standard to be applied to clinical trials in emergency situations with regard to single subjects. Differently, the US CFR provides that lower standards for informed consent can be applied not only in case of single subjects but also in the face of military operations and public health emergencies.<sup>440</sup> Furthermore, the EU CTR provides for the possibility to obtain informed consent by simplified means in case of cluster trials (i.e. that require groups of subjects

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<sup>435</sup> Article 35.1(a)-(f), EU CTR 536/2014.

<sup>436</sup> 21 CFR 50.23 (a)(1).

<sup>437</sup> 21 CFR 50.23 (a)(2).

<sup>438</sup> 21 CFR 50.23 (a)(3).

<sup>439</sup> 21 CFR 50.23 (a)(4).

<sup>440</sup> 21 CFR 50.23. The only way in which the EU CTR addresses the issue of public health crisis is by stating the following in the preamble: "[i]n the event of a public health crisis, Member States should have the possibility to assess and authorise a clinical trial application swiftly. No minimal timelines for approval should therefore be established." Preamble (8), EU CTR 536/2014.

rather than single participants, are low-intervention, use products in accordance with marketing authorizations, and justify the reliance on informed consent obtained in simplified means) when they take place in only one Member State.<sup>441</sup> Such option is not envisaged in the US context.

*(ii) Heightened Informed Consent Standards*

In certain circumstances, particular concerns arise in the case of participants in clinical trials that belong to potentially vulnerable categories. They regard subjects that are capable of giving informed consent but in certain conditions may not be able to freely exercise that capability i.e. persons performing military service, persons deprived of liberty, persons living in residential care institutions, etc., and also subjects that may have an impaired consent capacity e.g. incapacitated subjects and minors.

The EU CTR provides directly for specific norms for informed consent to be applied when the following subjects are involved in clinical trials: incapacitated subjects, minors, and pregnant or breastfeeding women.<sup>442</sup> It also lists some less direct recommendations regarding persons performing military service, persons deprived of liberty, persons living in residential care institutions, and anyone who belongs to an “economically or socially disadvantaged group or is in a situation of institutional or hierarchical dependency that could inappropriately influence her or his decision to participate.”<sup>443</sup> The US CFR provides for specific norms to be applied when children are involved in clinical trials and the FDA provides guidelines for cases involving incapacitated subjects. The US CFR also lists subjects to which general concerns apply: prisoners, pregnant women, and economically or educationally disadvantaged persons.<sup>444</sup> Hence, while the general set of subjects for which concerns are raised is almost identical in the EU and the US context, the subjects for which specific norms are to be applied differ in the two systems. Given this, it is only possible to compare the treatment reserved in the two legal frameworks to the only two categories for which they both developed specific norms (or, at least,

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<sup>441</sup> Article 30.3, EU CTR 536/2014.

<sup>442</sup> See respectively Article 31, 32, and 33, EU CTR 536/2014.

<sup>443</sup> Preamble (31) and (33), EU CTR 536/2014.

<sup>444</sup> 21 CFR 56.111 (a)(3).

guidelines: incapacitated subjects (“mentally disabled persons” in the US framework) and minors (children in the US framework).

As for incapacitated subjects, the EU CTR requires that informed consent is obtained by their representative, but that at the same time they are provided with information appropriate in view of their capacity.<sup>445</sup> More specific prescriptions require that their representative does not receive any incentive or financial inducement, that the trial is essential to the subject and the same data cannot be obtained through clinical trials conducted on subjects capable of giving consent, and that there are scientific grounds to expect a direct benefit for the subjects or some benefit for their population following the clinical trial.<sup>446</sup> Within the US framework, the duty to protect the interests of such vulnerable subjects is mainly left to the IRBs’ level. In this context, the FDA recommends e.g. that potential subjects’ capacity to give consent is assessed and that methods of enhancing the capacity to give consent are used.<sup>447</sup> In any event, informed consent norms refer to the need for representatives to be involved in giving consent on their behalf.<sup>448</sup> However, first, it appears clear that the EU system sets specific standards to be applied in the case of lack of capacity or diminished capacity of the subjects, while the US system finds in the IRBs the subjects that can most appropriately address vulnerability concerns. Second, interestingly, the EU framework clarifies that subjects with impaired capacity to consent can participate in clinical trials only when subjects with full capacity to consent cannot, while in the US framework such a clear-cut line is not established.

As to minors, it can be noted that they are the only category for which both systems provide a firm set of rules. In the EU, clinical trials on minors are subject to the following requirements: (1) consent of the minor’s representative, (2) information is given to the minor in an adequate way and from investigators experienced with children, (3) any wish of the minor not to participate is respected, (4) no incentives or financial inducement to the legal representative are given, (5) the clinical trial regards conditions that affect only children or aims at validating the use on children of data obtained on adults, (6) the trial

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<sup>445</sup> Article 31, EU CTR 536/2014.

<sup>446</sup> Article 31, EU CTR 536/2014.

<sup>447</sup> FDA, Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, 2014, at p. 35.

<sup>448</sup> E.g. “The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.” 21 CFR 50.20.

relates directly to a condition from which the minor suffers or can only be conducted on children, and (7) there are scientific grounds to expect a direct benefit for the subjects or some benefit for their population following the clinical trial.<sup>449</sup> If the minor reaches the age of legal competence during the clinical trial, his full informed consent is to be sought immediately.<sup>450</sup> In the US context, the two conditions under which children may be involved in clinical trials are: (a) no greater than minimal risk to children is presented and (b) “adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.”<sup>451</sup> Exceptions to the first condition can be made when the risk is justified by the anticipated benefit to the subjects and the benefit-risk ratio reaches the same level of other available treatments.<sup>452</sup> Interestingly, informed consent for clinical trials involving children (minors) can be obtained through child assent and paternal/guardian permission.<sup>453</sup> The possibility of obtaining the assent from children is assessed at the IRBs’ level, but the default option seems to require it. In fact, the US CFR specifically lists exceptions under which the assent of children is not to be sought.<sup>454</sup> The main two differences that can be observed regarding the requirement in the EU for the condition addressed in the clinical trial to specifically regard minors (to the extent that this is possible) and the eminent role for the assent of children in the US system.

#### *(5) Monitoring*

Following the approval of a clinical trial, institutional actors are generally entrusted with ensuring that all the stakeholders involved comply with the applicable legal standards. Two contexts in which a comparative analysis of the applicable monitoring provisions is

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<sup>449</sup> Article 32, EU CTR 536/2014.

<sup>450</sup> Article 32, EU CTR 536/2014.

<sup>451</sup> 21 CFR 50.51.

<sup>452</sup> 21 CFR 50.52. Note that a further exception to this standard can be allowed when “(a) The risk represents a minor increase over minimal risk; (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and (d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians (...)” 21 CFR 50.53.

<sup>453</sup> FDA, Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, 2014, at p. 37.

<sup>454</sup> 21 CFR 50.55 (c).

particularly interesting are those of reporting and inspections, and – especially in light of this contribution – the context of admissibility of data obtained through clinical trials conducted outside the territories of the regulating states. The next sections will address both categories of provisions.

*(a) Reporting and Inspections*

Once clinical trials have obtained approval to be conducted, the most relevant context in which human subjects are protected is within monitoring and inspections.

First, in both the US and the EU frameworks, clinical trials are subjected to constant monitoring. Under the EU CTR, sponsors must submit an annual report.<sup>455</sup> Similarly, under the US CFR, IRBs are expected to review clinical trials not less than once a year.<sup>456</sup>

Second, both legal frameworks provide for governmental inspections in order to ensure a high protection of human subjects. In the EU framework, two kinds of inspections are envisaged: the inspections conducted by Member States – of clinical trials that take place on their territory or in a third country – and the controls conducted by the European Commission to ascertain Member States’ compliance with the EU CTR.<sup>457</sup> Within the US framework, the FDA is directly in charge of conducting inspections. Specifically, sponsors and investigators are required to permit FDA investigators to access, copy, and verify any records or reports relevant to clinical trials.<sup>458</sup>

To conclude, both frameworks establish the need for annual reporting/monitoring and the possibility of governmental investigations, but at the EU level the latter are managed by Member States, while at the US level they are directly conducted by the FDA.

*(b) Admissibility of Foreign Data*

Given that both the EU and the US clinical trial legal frameworks consist of standards used in developed economies, in the context of this contribution it is relevant to present some observations as to how the two systems deal with results obtained in clinical trials conducted abroad (in particular, in developing economies).

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<sup>455</sup> Article 43, EU CTR 536/2014.

<sup>456</sup> 21 CFR 56.108 (a)(1) and 56.109 (f).

<sup>457</sup> Respectively, Article 78 and 79, EU CTR 536/2014.

<sup>458</sup> 21 CFR 312.68 and 812.145.

The first significant point regards the extent to which the issue is relevant in the two systems. Retrieving data on the phenomenon of the import of data obtained by foreign clinical trials, as well as on the extent to which those clinical trials are subject to inspection procedures ordered by US and EU (or, indirectly, Member States) institutions is not an easy task. Such figures are not regularly publicly disclosed, but official sources have provided them on some occasions in the last years. For example, the European Medicines Agency (EMA) disclosed that 61.9% of the patients in pivotal trials submitted in marketing-authorization applications to the Agency between 2005 and 2011 were from third countries.<sup>459</sup> Similarly, the FDA has noted that, in the period between 2001-2014, 80% of applications for pharmaceutical marketing authorization contained data from non-US studies, and that 78% of all clinical trials subjects were enrolled outside the US.<sup>460</sup> Both sets of figures support the idea that carrying out clinical trials “abroad” and importing the results obtained thereby is a relevant phenomenon in both systems. The amount of inspections conducted overseas, however, is still not proportionate to the extent of the phenomenon. For example, between 1997 and 2012, 46.5% of inspections were requested by the European Medicines Agency for sites in the EU/EEA/EFTA region, 26.05% for sites in North America, and 27.45% in the rest of the world.<sup>461</sup> Similarly – and despite the lack of analysis regarding identical time-periods – in 2013, FDA inspections regarded US sites in 70% of the cases and for example in 20% of the cases European-based sites.<sup>462</sup>

From the regulatory point of view, the EU and US legal framework use different *approaches* – to the extent that the US CFR addresses the issue more explicitly than the EU CTR and connected documents – but eventually establish similar *standards* – given that they both heavily rely on the Good Clinical Practice (GCP) framework.

As to the relevant sources, the EU CTR does not itself provide for a clear-cut rule on the admissibility of trials conducted in third countries. Instead, the EU standard emerges

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<sup>459</sup> Including 27.8% from the ROW region (Africa, Middle East/Asia/Pacific, Australia/New Zealand, Central/South America, CIS, Eastern Europe-non EU), and 34.1% from North America. European Medicines Agency, *Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency*, 2013, EMA/INS/GCP/676319/2012.

<sup>460</sup> Ayalew, *op. cit.*

<sup>461</sup> European Medicines Agency, *Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency*, 2013, EMA/INS/GCP/676319/2012.

<sup>462</sup> Ayalew, *op. cit.*

from a combination of various legal provisions and soft-law considerations. A series of references to third countries exists also in the EU CTR, but none of its provisions directly addresses the issue of data import.<sup>463</sup> The main sources in this context are the norms to which the EU CTR directly refers: Directive 2001/83/EC and Regulation (EC) No 726/2004 of the European Parliament and of the Council. Following those sources, clinical trials conducted in third countries outside of the EU/EEA and used in marketing authorization applications (or in applications for a Scientific Opinion under Article 58 of the Regulation (EC) No. 726/2004), “must be conducted on the basis of principles equivalent to the ethical principles and principles of good clinical practice applied to clinical trials in the EU.”<sup>464</sup> Interpretational issues arise when subjects are required to interpret and clarify the meaning and scope of “ethical principles and principles of good clinical practice.” In fact, a wide array of documents providing for ethical principles exists.<sup>465</sup> However, first, it is not clear to which extent their nature must be considered directly binding in the case of clinical trials conducted in third countries and, second, it is not clear how Member States are required to weigh those principles and enforce them. As to more immediately and univocally applicable standards, it can be noted that two set of provisions (the first being more binding in nature than the second, the second being more technical) are helpful in determining the scope and nature of the rules: the Good Clinical Practice Directive<sup>466</sup> and the considerations presented by the EMA in recent

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<sup>463</sup> E.g. Articles 42, 53, 74, and 78, EU CTR 536/2014.

<sup>464</sup> European Medicines Agency, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities, 2012, EMA/121340/2011.

<sup>465</sup> E.g. Ethical principles governing the conduct of clinical trials are set out in the Charter of Fundamental Rights of the European Union (2000), the Council of Europe’s Convention on Human Rights and Biomedicine (1997) and its Additional Protocol on Biomedical Research (2005), the Universal Declaration of Human Rights (1948), the Convention for the protection of Human Rights and fundamental Freedoms (1950), the United Nations’ Convention on the Rights of the Child (1989), the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005), the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997), the International Declaration on Human Genetic Data (UNESCO, 2003), the CIOMS-WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects (Geneva 2002), the Declaration of Helsinki of the World Medical Association (2008), Opinion 17 of the European Group on Ethics (2003) and the EU Ethical considerations for clinical trials on medicinal products conducted with the pediatric population (2008). See also Practical steps to implement ethical requirements are set out in the CPMP/ICH/135/95 guideline on Good Clinical Practice (1995) (ICH E6) and ICH E11 Note for guidance on clinical investigation of medicinal products in the pediatric population (2001). As noted in European Medicines Agency, *Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities*, 2012, EMA/121340/2011.

<sup>466</sup> Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the

consultations.<sup>467</sup> In particular, the latter provides instructions for several issues, such as ethics committees and national regulatory authority oversight, informed consent procedures, confidentiality standards, fair compensation, protection of vulnerable populations, use of placebo, access to treatment following the clinical trials, and applicability of data to the European population.<sup>468</sup> Additionally, in the EU context, three other sub-issues are currently relevant: the rules applicable in case of manufacturing or importing investigational medicinal products, Mutual Recognition Agreements (MRAs) and related agreements with third countries that regard the mutual acceptance of results of manufacturers' inspections, and the EU-FDA mutual recognition of inspections system which recently entered into force.<sup>469</sup> It is also worth noting that the sources listed so far – which are relevant in the EU context – have until now been interpreted and applied in combination with Directive 2001/20/EC;<sup>470</sup> given that the latter has been repealed by the EU CTR, it is likely that in the short term, following the full implementation of the EU CTR, clinical trials practice as well as EU jurisprudence may find that the standards to be applied to clinical trials conducted outside the EU are more clearly those established by the EU CTR for EU actors. This intuition is supported by the inclusion Article 79 in the EU CTR, which directly refers to Directive 2001/83/EC – specifically, to a provision included in the Directive which establishes that clinical trials conducted outside the EU relating to medicinal products intended to be used in the EU, shall be “designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC.”<sup>471</sup> Reading the provision updated to the implementation of the EU CTR will likely impose that the applicable standards are those equivalent to the new EU CTR. An additional observation in support of this finding regards Article 25 (5) of

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requirements for authorisation of the manufacturing or importation of such products (the “GCP Directive”).

<sup>467</sup> Above all, the European Medicines Agency, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities, 2012, EMA/121340/2011.

<sup>468</sup> Ibid.

<sup>469</sup> “Quality of medicines and Good Manufacturing Practices (GMP) - Public Health - European Commission.” Public Health, 30 Nov. 2017, ec.europa.eu/health/human-use/quality\_en.

<sup>470</sup> Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (the “Clinical Trial Directive”).

<sup>471</sup> Articles 79, EU CTR 536/2014.

the EU CTR, which provides that foreign clinical trials (when their results are used in the context of an EU application) must have been conducted in accordance with principles equivalent to those of the EU CTR itself “as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial.”<sup>472</sup> Future jurisprudence and institutional actions may help to clarify whether such a standard may actually be read *a contrario* as requiring that not all standards set in the EU CTR must be respected by EU-regulated foreign clinical trials, but only those regarding the protection of subjects and data quality. To conclude, as to the EU framework, it can be noted that it is clearly established that the results of clinical trials conducted in third countries may be used in EU applications when GCP standards are met; however, GCP standards may be of difficult identification and interpretation due to their often general nature, and (ii) in any event the reliance on GCP standards does not necessarily impose on sponsors the duty to comply with each single provision of the EU CTR, at least until further jurisprudence and institutional action helps to clarify this aspect.

The US CFR provides for a more specific tandem of norms to be applied to data obtained via clinical trials conducted overseas. Interestingly, the set of rules distinguishes clearly two sub-categories of situations: (a) the case of foreign clinical studies not conducted under an IND and (b) the narrower case of an application for marketing approval based solely on foreign clinical data.<sup>473</sup> (i) In the former case, the FDA accepts “well-designed and well-conducted foreign clinical study (i.e. clinical trial) not conducted under an IND” provided that two conditions are met.<sup>474</sup> First, the clinical trial must have been conducted in accordance with GCP.<sup>475</sup> This standard is the same as set out in the EU framework and potentially has the same limits to the extent that no fixed set of standards is contextually listed in the norm. And second, the FDA is able to conduct on-site inspections if

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<sup>472</sup> Articles 25.5, EU CTR 536/2014.

<sup>473</sup> Respectively 21 CFR 312.120 and 21 CFR 314.106.

<sup>474</sup> 21 CFR 312.120 (a).

<sup>475</sup> The US CFR defines what GCP represents in the context of such provision: “For the purposes of this section, GCP is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected. GCP includes review and approval (or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating a study, continuing review of an ongoing study by an IEC, and obtaining and documenting the freely given informed consent of the subject (or a subject’s legally authorized representative, if the subject is unable to provide informed consent) before initiating a study.” 21 CFR 312.120 (a)(i).

necessary.<sup>476</sup> This second aspect seems to be stricter than the parallel EU standard. In fact, while several provisions in the EU context envisage the possibility of inspections to be conducted in third countries,<sup>477</sup> the possibility of running such inspections is not explicitly listed as a requirement for the admission of foreign data. (ii) In the case of applications based solely on data obtained by foreign clinical trials, the US CFR establishes heightened scrutiny. In particular, applicants must prove that: (1) the data is applicable to the US population and medical practice; (2) the clinical trials have been performed by clinical investigators of recognized competence; and (3) the data may be considered valid without the need for on-site inspection (or the inspection may nevertheless be conducted, if necessary).<sup>478</sup> The presence of a narrower case such as the one described is not given in the EU framework, especially with regard to the first requirement. In this context, however, it is worth noting that EMA's recommendations suggest applicants take similar aspects into consideration.<sup>479</sup> To conclude, in the framework of US legislation, the ultimate standard applicable to foreign clinical trials is generally that of GCP, similarly to what is established in the EU framework. However, (i) the requirement of accessing sites for inspections is more prominent than in the EU context, (ii) the case of applications based solely on foreign data is directly regulated, and (iii) in the latter case, applicability of the data to the US population is a *sine qua non* condition.

Given that a common issue in both the EU and the US framework is the identification of clear obligations arising from the reliance on GCP standards, it is worth noting that substantial improvements in the context of collegial identification and mutual recognition

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<sup>476</sup> 21 CFR 312.120 (a)(ii).

<sup>477</sup> E.g. Article 78, EU CTR 536/2014: “[i]n order to efficiently use the resources available and to avoid duplications, the Agency shall coordinate the cooperation between Member States concerned on inspections conducted in Member States, in third countries, and inspections conducted in the framework of an application for a marketing authorisation (...);” Article 21, Directive 2005/28/EC: “[t]he inspectors shall be familiar with the procedures and systems for recording clinical data, and with the organisation and regulation of the healthcare system in the relevant Member States and, where appropriate, in third countries;” and Article 44, Regulation (EC) No 726/2004: “the Commission may, upon receipt of a reasoned request from a Member State or from the said Committee, or on its own initiative, require a manufacturer established in a third country to submit to an inspection.”

<sup>478</sup> 21 CFR 314.106 (b).

<sup>479</sup> Cf. Applicants are invited to take into consideration the applicability of the proposed indication and the therapeutic needs of the European population as noted in European Medicines Agency, *Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities*, 2012, EMA/121340/2011

of such obligations are constantly fostered. The two main potential sources of development in such contexts is the progress under the EU-US mutual recognition of inspections of medicines manufacturers system<sup>480</sup> and the ICH E6 Good Clinical Practice (GCP) Guideline.<sup>481</sup> In particular, the latter provides for a unified standard for the EU, the US and other states (Japan, Canada, and Switzerland) to facilitate the mutual acceptance of data from clinical trials by the regulatory authorities in these jurisdictions.<sup>482</sup> Its most updated version has been implemented by the EMA in December 2016<sup>483</sup> while implementation in the US is still pending. The evolution of the status of both policies in the EU and US framework remains a major issue to be observed in the next months.

### III. Preliminary Conclusions

To conclude, the comparative analysis presented in this chapter aimed at providing an overview of the current legal regime of clinical trials in the EU and the US.

On the one hand, the analysis presented insights for future researches on the two regimes and the requirements that stakeholders are expected to comply with. Such insights, while descriptive in nature, can be deemed to be particularly relevant given that an analysis of this kind has not yet been developed and, furthermore, considering that the EU CTR here studied sets new precise rules to be applied in the EU context, and has not yet been comprehensively studied in literature. In particular, this contribution has focused on describing how the following elements are addressed in the EU clinical trials legal framework and in that of the US: some fundamental preliminary elements – including definitions, principles, mechanisms for the delegation of competences, competent

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<sup>480</sup> In June 2017, the European Commission confirmed that the FDA has “the capability, capacity and procedures in place to carry out good manufacturing practice (GMP) inspections at a level equivalent to the EU” and in October 2017 the FDA confirmed the capability of eight EU Member States (Austria, Croatia, France, Italy, Malta, Spain, Sweden, and United Kingdom). See “EU-US mutual recognition of inspections of medicines manufacturers enters operational phase.” *European Medicines Agency - News and Events - EU-US mutual recognition of inspections of medicines manufacturers enters operational phase*,

[www.ema.europa.eu/ema/index.jsp?curl=pages%2Fnews\\_and\\_events%2Fnews%2F2017%2F10%2Fnews\\_detail\\_002842.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fnews_and_events%2Fnews%2F2017%2F10%2Fnews_detail_002842.jsp&mid=WC0b01ac058004d5c1).

<sup>481</sup> “Efficacy Guidelines.” *ICH*, [www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html](http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html).

<sup>482</sup> *Ibid.*

<sup>483</sup> European Medicines Agency, Guideline for good clinical practice E6 (R2), Step. 5, Committee for Human Medicinal Products, 2016, EMA/CHMP/ICH/135/1995.

authorities, and some exceptions (clinical studies not subject to clinical trials regulations or only subject to them in a limited way); the scope and technical aspects of the applications that sponsors are required to submit to governmental authorities in order to obtain an authorization to conduct clinical trials – including a comparison of each element of such application e.g. cover letter/sheet, protocols, IB, technical information on chemistry, manufacturing, and control, protection of human subjects and informed consent practices; the assessment mechanisms – including issues such as their timing, the bodies entrusted with the assessment, the applicable criteria, and the possible outcomes of the process; some additional issues that focus particularly on concerns connected with the protection of human subjects in clinical trials – including the reliance on placebo-controlled clinical trials and the rules applicable to informed consent practices; finally, the monitoring mechanism provided in each legal framework – including, in particular, consideration on issues such as reporting, inspections, and admissibility of data acquired via clinical trials conducted outside the territory of the EU or the US.

On the other hand, the analysis presented in this chapter allows for the presentation of some conclusions more specific to the goal of providing an educated opinion on the similarities and differences of the EU and US clinical trials policy and legislation and their capability to influence other attempts to regulate clinical trials at the international level or in other countries (as models). In particular, the analysis presented here supports the following three general findings.

First, the ways in which the EU and the US regulate clinical trials are extremely similar as of the goals and elements of the regulation and the standards of protection ensured to human subjects that take part in clinical trials. Despite the presence of slightly different standards and approaches in the two frameworks, the analysis presented did not identify extremely divergent elements in the two sets of provisions observed.

Second, nevertheless, a main difference between the two systems exists, deriving from the institutional structure of the EU and the US. In the US context, non-governmental actors (IRBs) are entrusted by the legislator with the task of approving and supervising clinical trials; in the EU context, governmental actors (Member States) are entrusted by the legislator with the task of approving and supervising clinical trials. As of the final decisional power, however, it can be noted that in the US, such power is reserved to a federal governmental agency (the FDA) and in the EU it remains allocated to the level

of the Member States (despite the fact that they must act in compliance with criteria established at the EU level). Potentially, as a consequence of the allocation of powers just described, as well as a consequence of the fact that the EU CTR has not entered its final phase of full implementation yet, the level of information available to stakeholders in the two systems (in quantitative terms) is not equal. In particular, the possibility for stakeholders of consulting the numerous guidelines produced by the FDA renders the US clinical trials regulation more accessible to users.

Third, it is important to note how the choices of both the EU and the US legislator confirm the interests and concerns already identified in this thesis with regard to clinical trials conducted at the global level. In fact, in both legal frameworks references to international standards (e.g. ICH guidelines), efforts to address challenges connected with the globalization of clinical trials (e.g. admissibility mechanism for data obtained via foreign clinical trials), and practical attempts to value cooperation between various national and international institutions can be found. Nevertheless, it is relevant to highlight how both systems chose to address such issues relying on a combination of approaches – that may often render the stakeholders’ activity of identification of the precise norms to be applied and respected more complex – in certain cases implementing international standards in their legislation directly, thereby awarding them fully binding power, and in other cases “merely” including broad references to those standards. In this context, it can be expected that further legislative developments both at the EU and at the US level will concentrate on the challenges provided by those standards in the context of practical implementation and compliance.

Table 2 summarizes the core finding of the comparative analysis presented in this chapter.<sup>484</sup>

Table 2 Prominent Comparative Elements		
	EU legal Framework	US legal framework
Def: Clinical Trials	Investigation on HS Object are clinical trials (seen as sub-category of clinical studies)	Investigation on HS Object are clinical investigations

<sup>484</sup> Note that in the table HS stands for human subjects, MS stands for Member States, IB stands for investigator’s brochure, and IC stands for informed consent.

	Variety of aims (mainly safety and efficacy)	Aim at approval for commercialization
Def: Sponsor	Open generic	List of traditional sponsors (not closed)
Def: Investigator	Default: team-member (principal investigator is the leader)	Default: team-leader (sub investigator is the team-member)
Def: Subject	Control or non-control group	Control or non-control group
Principles	Protection of human subjects and the interest in scientific validity	Protection of human subjects and the interest in scientific validity
Delegation of competences under	Subsidiarity and proportionality	Interstate commerce clause
Competent authorities to receive the application	MS through the EU Portal	FDA
Exceptions	Low-interventional clinical trials must still file an application but are subject to less stringent rules	Investigations similar in nature to the EU low interventional clinical trials are exempted from the duty to apply
Cover letter/sheet	Associated with EU application form	Associated with introductory information
Protocols	Extensive list of elements	Distinction on the basis of the CT's phases
IB	No explicit reference to side effects Mandatory non promotional form	Explicit reference to side effects
Chemistry, manufacturing, and control	Narrow list of elements Envisages case of products already approved/commercialized abroad	Extensive list of elements Envisages case of products already approved/commercialized abroad
Subjects and IC	Addressed in application-related norms	Addressed under a specific and separate category of norms
Assessment timing	ca. 55 days	ca. 30 days
Bodies entrusted with assessment	Ethic committees in MS Mandatory laypersons involvement	Two tiers: IRBs and FDA Diversity concerns
Assessment criteria	Single set of criteria provided to MS	Two sets of criteria provided: one for the IRBs' level and one for the FDA's level  Explicit reference to list of vulnerable subjects to be

		protected from risks of coercion and undue influence
		Distinction on the basis of CT phases
Possible outcomes	Classical approval-rejection mechanism	Exception granted or imposition of clinical hold
Use of placebo	Not prohibited but limited on the basis of risk-considerations	Not prohibited but in practice used mainly for add-on treatments
IC	Understandability as core concept  Must include possibility of damage compensation and information on involuntary termination	Understandability as core concept  Short and long forms available and optional elements can be included
Lowered IC standards	Emergency situations Cluster trials	Emergency situations Military operations and public health emergencies
Hightened IC standards	Specific norms for: incapacitated subjects, minors, and pregnant or breastfeeding women  General concerns for: persons performing military service, persons deprived of liberty, persons living in residential care institutions, economically/socially disadvantaged subjects	Specific norms for: children plus FDA Guidelines for: incapacitated subjects  General concerns for: prisoners, pregnant women, and economically or educationally disadvantaged persons
Reporting	Yearly reporting	Yearly reporting
Inspections	Managed by MS	Managed by the FDA
Admissibility of foreign data	GCP standards apply	GCP standards apply  Distinction: studies based only on foreign data, studies not based only on foreign data  Prominent role of need for access to sites for inspections  Applicability of data to US population for foreign-data-only studies is mandatory

IV. Addendum on the Implementation Framework of the EU Clinical Trials Regulation

As noted above, this contribution is elaborate although the complete implementation of the EU CTR is still pending. On the one hand, the status of such implementation within

Member States' current clinical trials assessment-systems is not publicly known. On the other hand, even following the entry into force of the EU CTR, it can be presumed that differences among the different assessment-systems between Member States will exist (e.g. with regard to ethics committees, given that the EU CTR does not regulate many aspects of their functioning). Therefore, in order to provide insights on those issues, this addendum will present the results of a series of questions submitted to Member States. Despite the lack of statistical value of the results, they can nevertheless be seen as providing input on the issues highlighted so far in this analysis.

*(1) Presentation of the Sample*

The first step taken in this part of the activity regarded the identification of contacts for Member States. This goal was achieved by compiling a list of the national authorities that enforce clinical trials regulations in each Member State and verifying it using the list of contact points provided by EMA.<sup>485</sup> An individual email was sent to each contact point to assess its availability to respond to questions related to the clinical trials' legal framework in the respective Member State. Following these approaches, four contact points (representing four Member States) agreed to participate in the survey/interviewing process. Preliminarily, it can be noted that the contact points that eventually participated in the activity are employed by the national competent authorities of Cyprus, Latvia, Lithuania, and Norway.<sup>486</sup>

*(2) Presentation of the Survey*

Each contact point was provided a list of 23 questions. For some questions, the four contact points were asked to select one answer among an available set of alternatives. In any event, they were given the possibility to clarify their answers by adding further comments. Table 3 lists the topics addressed by each main question (and set of sub-questions).

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Table 3	
Survey Submitted to Clinical Trials Contact Points for EU Member States	
(Topics addressed by each question)	
Question 1	Contact details and Member State

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<sup>485</sup> EudraCT, National Competent Authorities Clinical Trials Contacts, EMA/438927/2008.

<sup>486</sup> Note that despite the fact that Norway is not technically an EU Member States, it is still expected to comply with the EU CTR due to the relevance of such regulation for EEA Member States (see the title of the EU CTR which reads “text with EEA relevance”).

Question 2	Opinion on the tendency of clinical trials to have an international dimension
Question 3	Mechanism used in the Member State to approve clinical trials. With sub-questions on e.g. proportionality of the oversight' invasiveness with the clinical trials' invasiveness, protection of vulnerable subjects, etc.
Question 4	Availability of clinical trials regulatory materials in languages different than the one of the Member State
Question 5	Relationship of the daily operation of clinical trials supervision in the Member State with the EMA's operate
Question 6	Means of human subjects' protection and data reliability implemented in the Member State.
Question 7	Opinion on registration and reporting of clinical trials' results practices in the Member State.
Question 8	Existence of application fees for sponsors and costs for human subjects.
Question 9	Opinion on the status of the EU CTR implementation.

### (3) Results

The first set of questions regarded the general approach of each Member State towards the internationalization of clinical trials. According to the contact points, all four Member States consider the involvement of a plurality of states in clinical trials a positive factor. However, given the choice between the involvement of EU countries only *or* EU and non-EU countries, two states considered the first option preferable to the second.<sup>487</sup>

As to the mechanism used in the Member States to approve clinical trials, the first relevant piece of information disclosed by the contact points regards the structure of the decision of competence in that context. This element is particularly interesting in the context of this contribution, given that the EU CTR grants Member States the power to decide how to structure their approval system, enabling the hypothesis that fragmentation between Member States will persist. On the basis of the information provided by the four contact points, it can be noted that all four Member States rely on the involvement of one or more governmental agencies as well as of one or more ethics committees.<sup>488</sup> Three of the four Member States calibrate the invasiveness of clinical trials' oversight with the level of intervention that the treatment being tested entails.<sup>489</sup> All four states require sponsors to pay an application fee. As to the availability of materials in languages

<sup>487</sup> The Member States being Lithuania and Norway.

<sup>488</sup> In particular, Lithuania relies on ethics committee, Cyprus on the National Bioethics Committee, and Norway, in addition to the Norwegian Medicines Agency involves the Directorate of Environment in the case of clinical trials entailing the use/testing of GMOs.

<sup>489</sup> The Member States being Latvia, Lithuania, and Norway.

different than the one of the Member State, questions to the contact points focused on the existence of materials in English. All four Member States provide forms for and/or allow the submission of materials in English (however, variability exists with regard to which forms are available in English). Finally, when asked whether their Member State involves patients/patents' organizations in the process of authorization of clinical trials, three contact points answered negatively and one affirmatively.<sup>490</sup>

With regard to the protection of vulnerable subjects, all four Member States require extra steps to be taken in the case of authorization and control procedures that involve vulnerable subjects. However, the identification of the categories to be deemed vulnerable is not uniform; in particular, in all four Member States two categories of subjects are univocally considered vulnerable: patients affected by mental health conditions and minors. This is consistent with the heightened scrutiny imposed in the case of clinical trials involving incapacitated subjects and minors under the EU CTR.<sup>491</sup> Two out of four Member States consider also pregnant women, breastfeeding women, and residents in residential facilities (e.g. nursing homes) vulnerable subjects.<sup>492</sup> This is clearly an issue on which all states will be expected to act upon as soon as the EU CTR fully enters into force, given that the EU CTR explicitly awards heightened protection standards to pregnant women and breastfeeding women.<sup>493</sup> As to clinical trials that focus on very rare diseases,<sup>494</sup> that under the EU CTR should be fostered, it can be noted that none of the interviewed Member States provides for incentives for such clinical trials.

As to registration and reporting, two member States (Lithuania and Latvia) rely on a national clinical trial registry; results are usually reported to the competent authority within one year.<sup>495</sup>

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<sup>490</sup> Cyprus and Latvia answered negatively and Norway clarified that its Medicines Agency does not but it is aware of the fact that the European Commission may do so. Lithuania answered affirmatively. This may be seen as conflicting – at least in principle – with the EU CTR. The latter reads: “[w]hen determining the appropriate body or bodies, Member States should ensure the involvement of laypersons, in particular patients or patients’ organisations.” Preamble (18), EU CTR 536/2014.

<sup>491</sup> Articles 30 and 31, EU CTR 536/2014.

<sup>492</sup> Specifically, Latvia and Lithuania awards particular protection to residents in residential facilities; Latvia and Norway do the same for pregnant women and breastfeeding women. At the same time, Cyprus is the only Member State that declared to award specific protection to elderlies.

<sup>493</sup> Article 32, EU CTR 536/2014.

<sup>494</sup> Preamble (9), EU CTR 536/2014.

<sup>495</sup> Note that in the case of Latvia results are reported directly in the EudraCT database.

With regard to the recruitment of human subjects and obtaining informed consent, it is worth noting that only the contact point for Norway declared that its Member State provides a preferential authorization procedure in place for clinical trials, which plan to recruit subjects on its territory and have already obtained authorization in another Member State. It is notable also that Cyprus is the only one of the four Member States not requiring interviewers in the recruitment process to take the social status of prospective subjects into consideration during the interviewing process. In all four Member States, participants are not allowed to pay for investigational medicinal products, auxiliary medicinal products, or medical devices used for their administration and procedures required by clinical trials. Furthermore, none of the four Member States provides for a minimum amount of time that must lapse between the presentation of the clinical trial to subjects and obtaining their informed consent.<sup>496</sup> However, this does not necessarily imply a misalignment with the EU CTR's informed consent regulation.<sup>497</sup> As of the subjects allowed to perform recruitment interviews, three of the Member States limit the possibility to perform such interviews to medical doctors.<sup>498</sup>

Finally, with regard to the transition between Directive 2001/20/EC and the EU CTR, all four contact points declare that the national legislation and standards in use in their Member State are still subject to revision (and do not meet the EU CTR standards yet).

To conclude, despite the lack of statistical value of this analysis, it can be noted that in the case of the Member States pooled – at least according to the answers provided during the interaction with contact points at their national clinical trials competent authorities – , on the one hand, a common interest in the supra-national regulation of clinical trials exists. And on the other hand, variability exists between some of the standards applied in different Member States. In the light of the entry in to force of the EU CTR, it is likely that such variability will decrease and that specific aspects of national legislations will be reformed (e.g. the protection of pregnant or breastfeeding women, the involvement of patients or patients' organizations in the authorization process, the fostering of clinical trials focused on ultra-rare disease, etc.).

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<sup>496</sup> Lithuania specified that “the time should be sufficient.”

<sup>497</sup> Cf. Article 29, EU CTR 536/2014 which reads: “[a]dequate time shall be given for the subject or his or her legally designated representative to consider his or her decision to participate in the clinical trial.”

<sup>498</sup> Norway allows it also to other medical professionals (e.g. registered nurses).



## CHAPTER SIX: CLINICAL TRIALS REGISTRIES – SUCCESSFUL GLOBAL DYNAMICS IN CLINICAL TRIALS REGULATION

### I. Introduction

Clinical trials registries are databases of privately and publicly funded clinical studies conducted within single countries or worldwide. Understanding their rationale, history, and functioning is particularly interesting in the context of this contribution. In fact, the development of clinical trials registration standards is one of the aspects of clinical trials regulation in which both (i) the *global dimension* is evident and extremely relevant and (ii) in a twenty-year span, the development of an international set of standards has been successfully achieved, thanks to the *interaction* of different stakeholders and both private and public actors.

The following sections will present an overview of the competing interests that stands behind the creation of clinical trial registries, of the history and functional characteristics of the principal registries, and some of the challenges still unresolved in the current status of clinical trial registries.

### II. Clinical Trials Registries and Competing Interests

Understanding the rationale and the – sometimes competing – interests behind the institution and implementation of clinical trial registries is necessary in order to better observe the dynamics that affect the registries and to regulate their evolution.

On the one hand, the arguments in favor of clinical trials registration often relies on four positive effects that widespread registration can produce. First, clinical trials registration – especially in macro-regional and international registries – results in increased *accessibility* of clinical trials information.<sup>499</sup> Increased accessibility has positive implications both for researchers and policymakers that are “making use of the

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<sup>499</sup> Cf. Pansieri, Claudia, et. al. “Clinical Trial Registries: More International, Converging Efforts are Needed.” *Trials* 18.1 (2017): 86.

information that is collected and made publicly available by clinical trial registries”,<sup>500</sup> and for human subjects that can take better decisions regarding their participation and can be rewarded for their altruistic choice to participate in clinical trials.<sup>501</sup> Second, clinical trials registration increase *transparency*.<sup>502</sup> The latter serves, among others, the interest of the scientific community, lowering the risk of “publication bias” and selecting publication and increasing access to pools of patients for recruitment purposes.<sup>503</sup> Selective publication is the phenomenon under which studies with positive results are publicized by publication and negative outcomes are more easily hidden from the scientific community and the public eye. Third, clinical trials registration enhances *standardization* in clinical trials.<sup>504</sup> And, in this context, standardization has both a global scale – which positively matches the current global dimension of clinical trials matters – and a positive impact on the protection of human subjects.

On the other hand, three concerns are generally presented by detractors of the implementation of increasingly stringent registration requirements. First, a concern for the *bureaucratic burden* derived from compliance requirements can be observed.<sup>505</sup> In substance, the risk connected with such a burden would be to make clinical research harder to conduct, instead of fostering it.<sup>506</sup> Second, a concern shared by both participants and sponsors regards the protection of *privacy interests* – specifically, in the form of concerns for participant safety regarding the risk of re-identification of depersonalized data.<sup>507</sup> Third, primarily among sponsors, there is a widespread concern for the risks connected with a potential *loss of competitive advantage*. This is the result of concerns

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<sup>500</sup> Viergever, Roderik F., and Keyang Li. “Trends in Global Clinical Trial Registration: An Analysis Of Numbers of Registered Clinical Trials in Different Parts of the World From 2004 To 2013.” *BMJ open* 5.9 (2015): 7.

<sup>501</sup> De Angelis et al., *op. cit.*

<sup>502</sup> Cf. Viergever and Li. *op. cit.* And Sim, Ida, et al. “Clinical Trial Registration: Transparency Is the Watchword.” *The Lancet* 367.9523 (2006): 1631-1633.

<sup>503</sup> See Simes, Robert J. “Publication Bias: The Case for an International Registry of Clinical Trials.” *Journal of Clinical Oncology* 4.10 (1986): 1529-1541.

<sup>504</sup> Cf. Pansieri, *op. cit.*

<sup>505</sup> *Ibid.*

<sup>506</sup> Sim et al., *op. cit.*

<sup>507</sup> Cf. Skoog, M., et al. “Transparency and Registration in Clinical Research in the Nordic Countries.” *Nordic Trial Alliance, NordForsk* (2015): 1-108. Note that despite the focus of the publication on a few countries, the concerns there expressed seem to be consistent with those generally identified and voiced at the international level.

for the protection of commercial interests such as intellectual property-related issues and ownership of the information produced via clinical trials.<sup>508</sup> Additional concerns regard the challenges that currently undermine the full implementation of clinical trials registration and potential; such challenges will be addressed later in this contribution. Nevertheless, the presentation of the competing interests – the case in favor of clinical trials registration and the one against it – remains a fundamental step to better understanding clinical trials registration regulation and evolution.

### III. Creation and Functioning of Clinical Trials Registries

This section aims at presenting the “historical” evolution of clinical trials registration – with a specific focus on the events that lead to the creation of the International Clinical Trials Registry Platform (ICTRP) and the functioning of the ICTRP.

Preliminarily it can be noted that clinical trials registration is supported by several legal authorities – both at the international and the national level.<sup>509</sup> In particular, the creation and implementation of clinical trials registries is consistent with the Declaration of Helsinki requirement that “[e]very research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.”<sup>510</sup> The Declaration of Helsinki provides also that

“[r]esearchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers (...) are accountable for the completeness and accuracy of their reports. (...) Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication.”<sup>511</sup>

Chronologically, the first operative clinical trial registry was introduced in the US in the late 1990s: in 1997, the US Congress introduced a set of rules requiring clinical trials

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<sup>508</sup> Cf. *Ibid.* And Zarin, Deborah A., and Tony Tse. “Moving Towards Transparency of Clinical Trials.” *Science* 319.5868 (2008): 1340.

<sup>509</sup> See, e.g. *ibid.*

<sup>510</sup> Article 35, World Medical Association (WMA). Declaration of Helsinki. Ethical principles for Medical Research Involving Human Subjects. *op. cit.*

<sup>511</sup> Article 36, *ibid.*

registration.<sup>512</sup> Following that, in 2000, the National Institutes of Health launched the online platform ClinicalTrials.gov.<sup>513</sup> Interestingly, several commentators have noted how the creation of the registry and its implementation resulted from the pressure produced by two actions: the lawsuit against GSK by New York State Attorney General Eliot Spitzer, and the endorsement of a comprehensive registry by the American Medical Association (AMA).<sup>514</sup>

It is worth noting, however, that it is not until a later crucial decision of the International Committee of Medical Journal Editors (ICMJE) that the registration rate started to clearly and steeply increase.<sup>515</sup> In particular, in 2004, the ICMJE published an editorial note acknowledging the role of patients' altruism in advancing clinical research and the widespread concern for selective publication.<sup>516</sup> The editorial note identified clinical trials registration as a means for promoting necessary transparency in clinical trials and announced that the ICMJE from mid-2005 on would have only considered for publication studies developed on the basis of clinical trials prospectively registered on a free of charge and publicly accessible registry.<sup>517</sup> The editorial note specified that, first, the registry should have respected a list of characteristics and, second, by that time, only the platform ClinicalTrials.gov complied with those requirements. To meet the ICMJE-standard, registries had to: (i) be accessible to the public at no charge; (ii) be open to all prospective registrants and managed by a not-for-profit organization; (iii) provide for "a mechanism to ensure the validity of the registration data;" (iv) be electronically searchable; (v) include at minimum the following information:

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<sup>512</sup> Food and Drug Administration Modernization Act (FDAMA), enacted Nov. 21, 1997, amended the Federal Food, Drug, and Cosmetic Act relating to the regulation of food, drugs, devices, and biological products.

<sup>513</sup> "Press Release: National Institutes of Health Launches "ClinicalTrials.Gov"." *US National Library of Medicine, National Institutes of Health*, [www.nlm.nih.gov/archive/20040831/news/press\\_releases/clntrlpr00.html](http://www.nlm.nih.gov/archive/20040831/news/press_releases/clntrlpr00.html).

<sup>514</sup> See Turner, Erick H. "A Taxpayer-Funded Clinical Trials Registry and Results Database." *Public Library of Science (PoLS) Medicine* 1.3 (2004): e60. And Steinbrook, Robert. "Public Registration of Clinical Trials." *New England Journal of Medicine* 351.4 (2004): 315-317. For the AMA declaration see Council on Scientific Affairs, American Medical Association. *Featured CSA report: influence of funding source on outcome, validity, and reliability of pharmaceutical research (A-04)*. June 2004.

<sup>515</sup> For data on the increase in registration trends see, e.g. the analysis provided in Viergever and Li, *op. cit.* as well as Viergever, Roderik F., and Davina Ghersi. "The Quality of Registration of Clinical Trials." *Public Library of Science (PoLS) One* 6.2 (2011): e14701.

<sup>516</sup> De Angelis, *op. cit.*

<sup>517</sup> *Ibid.*

“a unique identifying number, a statement of the intervention (or interventions) and comparison (or comparisons) studied, a statement of the study hypothesis, definitions of the primary and secondary outcome measures, eligibility criteria, key trial dates (registration date, anticipated or actual start date, anticipated or actual date of last follow-up, planned or actual date of closure to data entry, and date trial data considered complete), target number of subjects, funding source, and contact information for the principal investigator.”<sup>518</sup>

Although – as will be described later – nowadays, following some years of proliferation in the context of clinical trials registration, ClinicalTrials.gov is by far not the sole registry meeting those requirements, it is interesting to note that it has served as a practical basis for the creation of following registries, as it was the first one that had to be technically structured so as to contain enough information to serve the scientific community while preserving accessibility and transparency towards the general public – balancing the need for accuracy with recruitment-friendly features.<sup>519</sup> Above all, it can be noted how the platform has become so prominent: not solely following the implementation of binding rules and not solely following the inputs given by the scientific community, but as a result of *both sources of pressure* combined.

As mentioned above, ClinicalTrials.gov nowadays is not the only widely used and accepted clinical trials registry. It is actually one in a constellation of many, in which others are acceptable platforms even under the updated ICMJE standards.<sup>520</sup> Specifically, nowadays the ICMJE will consider for publication any study based on clinical trials prospectively registered on the ICTRP or any of the registries affiliated to the ICTRP.<sup>521</sup> In fact, the “most powerful boost” to clinical trials registration is represented by the establishment of the ICTRP in 2005.<sup>522</sup> The platform was formally launched in 2007 and provides users with a single access point to various national and regional registries.<sup>523</sup> In 2007, it was launched by the WHO, providing for a search portal providing a single point

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<sup>518</sup> Ibid.

<sup>519</sup> McCray, Alexa T., and Nicholas C. Ide. “Design and Implementation of a National Clinical Trials Registry.” *Journal of the American Medical Informatics Association* 7.3 (2000): 313-323.

<sup>520</sup> “Clinical Trial Registration—Looking Back and Moving Ahead.” Editorial, *New England Journal of Medicine*, June 28, 2017, 356.

<sup>521</sup> “Clinical Trial Registration.” ICMJE | Recommendations | Clinical Trial Registration, [www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html](http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html).

<sup>522</sup> Lemmens and Telfer, *op. cit.*

<sup>523</sup> Cohen, I. Glenn. *The globalization of health care: legal and ethical issues* (Oxford University Press, 2013) at p. 275.

of access to studies registered in various international registries.<sup>524</sup> As of October 2017, more than 390000 clinical trials were accessible through the platform.<sup>525</sup> Some relevant information regarding the ICTRP encompasses the following elements:

(1) Content-wise: the platform welcomes the prospective registration of clinical trials submitted to other national/regional registers.<sup>526</sup> Once trials are registered, they cannot be removed. (2) Quality- and validity-wise: the platform will not engage in controls and investigations itself. Instead, it relies on the sense of responsibility of registrants and national/regional registries to ensure that the person registering the trial and the trial exists and that the data submitted is complete.<sup>527</sup> (3) Accessibility-wise: the platform provides public access at no charge to content in English. It also guarantees access to search functions and the possibility to register trials at any time all year long.<sup>528</sup> (4) Data set-wise: currently, the platform lists 20 items that must be listed by a trial to be considered fully registered. The items include the primary registry and trial identifying number, the date of registration to the primary registry, any secondary identification number, the major source(s) of monetary or material support for the trial, primary and secondary sponsors, contacts for public and scientific queries, public and scientific title, the conditions studied and the interventions planned, key inclusion/exclusion criteria for participation in the study, the study type (e.g. randomized or non-randomized), the anticipated or actual date of the first enrollment, the target sample size, the recruitment status (e.g. trial still recruiting, suspended, or pending), primary and secondary outcomes of the study.<sup>529</sup> (5) Participation-wise: the ICTRP is a global platform emerged from a

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<sup>524</sup> “History, Policies, and Laws.” *ClinicalTrials.gov*, [clinicaltrials.gov/ct2/about-site/history](http://clinicaltrials.gov/ct2/about-site/history).

<sup>525</sup> Precisely, 456045 records were accessible for 390098 trials. The difference in the two figures is due to the fact that – as specified in the first page of the ICTRP’s search portal – “trials are sometimes recorded in more than one registry. These records can refer to each other using the ‘Secondary ID’ field. The search portal uses these Secondary IDs to group records about the same trial together in the search results.” See *ICTRP Search Portal*, [apps.who.int/trialsearch/Default.aspx](http://apps.who.int/trialsearch/Default.aspx). To read the number *vis a vis* figures that regard the entity of the registration phenomenon before the introduction of the ICMJE policy note, for example, that before the implementation of the policy *ClinicalTrials.gov*, the largest trial registry at the time, contained 13,153 trials (see Laine, Christine, et al., *op. cit.*)

<sup>526</sup> “WHO ICTRP Registry Criteria.” WHO, World Health Organization, <http://www.who.int/ictrp/network/criteria/en/>.

<sup>527</sup> “WHO ICTRP Registry Criteria.” WHO, World Health Organization, <http://www.who.int/ictrp/network/criteria/en/index1.html>

<sup>528</sup> “WHO ICTRP Registry Criteria.” WHO, World Health Organization, <http://www.who.int/ictrp/network/criteria/en/index2.html>

<sup>529</sup> “WHO Data Set.” WHO, World Health Organization, [www.who.int/ictrp/network/trds/en/](http://www.who.int/ictrp/network/trds/en/).

country-led initiative.<sup>530</sup> Therefore, it is up to national and regional institutions to decide whether to set primary registries for the trials that take place on their territory and whether to connect those primary registries with the ICTRP platform. Currently, the platform has 17 primary registries.<sup>531</sup> It lists also three partner registries that do not need to have a national/regional remit or the support of government, be managed by a not-for-profit agency, or be open to all prospective registrants; however, they must be “affiliated with either a Primary Registry in the WHO Registry Network or an ICMJE approved registry.”<sup>532</sup> As of the relationship between ICMJE standards and WHO standards, there seems to be a mutual exchange of standards (or the possibility of this exchange being a catch-22). In fact, according to the WHO, ICMJE approved registries – meaning those which meet the requirements set by the ICMJE, partially mentioned above in this section – are suitable for access to the ICTRP, while according to the ICMJE, the latter “is no longer the entity that reviews registries for acceptability (...) Registries that the WHO designates as primary registries will be acceptable to the ICMJE.”<sup>533</sup>

Similarly to other (primary) registries, the ICTRP has a double-folded goal. First, to foster access to trials, thereby increasing both the chances of recruitment and the access to the data produced by each trial.<sup>534</sup> Second, to increase the quality of registered data.<sup>535</sup> Interestingly, the ICTRP has also two other specific goals that are peculiar to the platform: first, to promote and support the creation of additional national/regional clinical

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<sup>530</sup> International Clinical Trials Registry Platform, WHO, World Health Organization, Brochure available at: [http://www.who.int/ict rp/ict rp\\_brochure\\_en.pdf?ua=1](http://www.who.int/ict rp/ict rp_brochure_en.pdf?ua=1)

<sup>531</sup> Australian New Zealand Clinical Trials Registry (ANZCTR), Brazilian Clinical Trials Registry (ReBec), Chinese Clinical Trial Registry (ChiCTR), Clinical Research Information Service (CRiS), Republic of Korea, Clinical Trials Registry - India (CTRI), Cuban Public Registry of Clinical Trials (RPCEC), EU Clinical Trials Register (EU-CTR), German Clinical Trials Register (DRKS), Iranian Registry of Clinical Trials (IRCT), ISRCTN, Japan Primary Registries Network (JPRN), Thai Clinical Trials Registry (TCTR), The Netherlands National Trial Register (NTR), Pan African Clinical Trial Registry (PACTR), Peruvian Clinical Trial Registry (REPEC), and Sri Lanka Clinical Trials Registry (SLCTR).

See: “Primary Registries.” WHO, World Health Organization, [www.who.int/ict rp/network/primary/en/](http://www.who.int/ict rp/network/primary/en/).

<sup>532</sup> “Partner Registries.” WHO, World Health Organization, [www.who.int/ict rp/network/partner/en/](http://www.who.int/ict rp/network/partner/en/). The partner registries are the following: Clinical Trial Registry of the University Medical Center Freiburg (affiliated to DRKS), DeReG - German Registry for Somatic Gene-Transfer Trials Affiliated registry (affiliated to DRKS), and Centre for Clinical Trials, Clinical Trials Registry – Chinese University of Hong Kong (affiliated to ChiCTR).

<sup>533</sup> “Clinical Trials Registration.” ICMJE | About ICMJE | Clinical Trials Registration, [www.icmje.org/about-icmje/faqs/clinical-trials-registration/](http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/).

<sup>534</sup> International Clinical Trials Registry Platform, WHO, World Health Organization, Brochure, *op. cit.*

<sup>535</sup> *Ibid.*

trial registries and/or the implementation of enforceable policies to incentivize the registration of trials that take place on their territory in any primary registry. Second, to specifically reduce the gap between the availability of information regarding trials registered/recruiting in high-income countries and those registered/recruiting in low- and middle-income countries.<sup>536</sup>

To conclude, nevertheless, it can be noted once again how the transition towards a more integrated and international dimension of clinical trials management and regulation – even if on a specific issue such as registration – provides observers with an example of back-and-forth inputs given by different stakeholders. Not only was the ICTRP created following the technical success of ClinicalTrials.gov (which was itself promoted by the editorial note of the ICMJE), but, following the introduction of the ICTRP, the ICMJE itself decided to adapt its definition of clinical trials to comply with the definition proposed by the WHO (the very same organization that gave birth to the ICTRP).<sup>537</sup> In a nutshell, the creation and success of clinical trial registries is the result of the constant and fluid interaction between norm-creators and the scientific community.

#### IV. Unresolved Challenges

Despite its core role in collecting and making clinical trials information available globally, the trend in favor of increasing clinical trial registration is not flawless. Improvement in the functioning of national/regional registries as well as in the ICTRP is sought both at the institutional level and within the scientific community. In fact, contributors to the field of clinical trials policy have identified the following concerns:

(i) First, *data quality and completeness*. As noted by Pensieri et al., the trial coverage of the ICTRP is constantly questioned and the number of trials conducted globally remains unknown.<sup>538</sup> In other words, while the growth of the registration trend is evident and can positively be read in light of striving for increased accessibility to clinical trials information, there are still many clinical trials that take place without being registered, and quantifying them is extremely difficult. Furthermore, even in the context of trials conducted in developed countries, quality of registered data remains a concern. For

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<sup>536</sup> Ibid.

<sup>537</sup> “Clinical trial registration—looking back and moving ahead.” Editorial, *op. cit.*

<sup>538</sup> Pensieri, et al., *op. cit.*

example, a study conducted by Chow found that in four years, out of 860 published trials randomly selected, only 102 were adequately registered.<sup>539</sup>

Technical issues that regulators should address include the need “to minimize inadvertent duplicate registrations, to ensure that interventions have unambiguous names, and to have a search engine that identifies all trials that meet a user’s specifications.”<sup>540</sup> Hence, Good compliance with the registration goal requires both the creation of the practical tools necessary (complex registries and platforms) and the implementation of compliance measures.

(ii) Second, the challenge of *lacking compliance*, especially in a context in which the proliferation of registries calls for a higher need for standardization.<sup>541</sup> As note by Viergever and Li following a comprehensive study of registration trends between 2004 and 2013, improvements in clinical trial registration have not been uniform at the global level.<sup>542</sup> Their contribution is particularly insightful because it provides evidence of the fact that the efficacy of implementation measures varies across the globe. For example, accordingly, while arguably the most effective measure is mandatory registration required by law, the registration rate has steeply risen in Europe and North America following the ICMJE’s announcement (described above) and in Asia following the implementation of local measures.<sup>543</sup>

Notably, measures that have proven to positively affect the registration trend include “enforcement of registration by funders, ethics committees and local journal editors; national policies and ethical guidelines that encourage trial registration; and self-regulation by universities and the pharmaceutical industry.”<sup>544</sup>

Consequently, any attempt to further incentivize and regulate clinical trials registration at the international level should not disregard that differences exist both in terms of the

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<sup>539</sup> Anesthesiologynews, Many Published Clinical Trials Inadequately Registered, October 2017,

<http://www.anesthesiologynews.com/Policy-and-Management/Article/10-17/Many-Published-Clinical-Trials-Inadequately-Registered/44782>

<sup>540</sup> Zarin, Deborah A., et al. “Issues in the Registration of Clinical Trials.” *Journal of the American Medical Association* 297.19 (2007): 2112-2120.

<sup>541</sup> Pansieri, et al., *op. cit.*

<sup>542</sup> Viergever and Li, *op. cit.*

<sup>543</sup> *Ibid.*

<sup>544</sup> Viergever and Li, *op. cit.*

“starting point” of different national/regional registries – as of registration rate, data quality, accessibility, etc. – and in terms of efficacy of specific policies e.g. guidelines for professional organizations, mandatory nation-wide registration, etc. For example, consistently with what was suggested by Dickersin and Rennie,<sup>545</sup> regulatory provisions could be implemented to require: (a) executive governmental agencies to take full responsibility to ensure trial registration within the territory of each state; (b) institutions and organizations that conduct clinical research (i.e. investigators) to register the trials that they are responsible for; (c) industry leaders (i.e. sponsors) to insist on comprehensive registration; incidentally, on the matter of industry-driven compliance with registration requirements, it is worth noting that pharmaceutical companies such as GSK committed to making information regarding its trials available through a private registry.<sup>546</sup> While the registry confirms GSK’s commitment to registration, first, it is still unclear whether it is beneficial for the general public and, second, the registry itself includes a disclaimer recommending professionals to “consult prescribing information approved in their country,”<sup>547</sup> suggesting that the registry mainly targets physicians willing to learn about GSK’s products, rather than patients and members of the scientific community. (d) Journal editors to implement the ICMJE standards more strictly and to require unique registration numbers for trial reports; (e) lawmakers to require ethics committees to deem registration mandatory.

(iii) Third, a further concern regards the *accessibility and searchability of results*. Two issues can be seen as belonging to this context.

First, the issue of reporting outcomes of completed but unpublished studies. Future policy and regulatory decisions should consider fostering complete reporting on clinical trials registries, to the benefit of future systematic reviews.<sup>548</sup>

The second issue regards data sharing. This aspect is expected to evolve in the next months as the ICMJE has recently updated its standards on data sharing statements for

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<sup>545</sup> Dickersin and Rennie, *op. cit.*

<sup>546</sup> “About the GSK Clinical Study Register.” *GSK Clinical Study Register*, [www.gsk-clinicalstudyregister.com/](http://www.gsk-clinicalstudyregister.com/).

<sup>547</sup> *Ibid.*

<sup>548</sup> Prayle, Andrew P., et al. *op. cit.*

clinical trials.<sup>549</sup> The new standards are consistent with the goals shared by the ICMJE and the WHO to achieve: universal prospective registration, public disclosure of results from all clinical trials, and data sharing.<sup>550</sup> Under the new standards: (1) “[a]s of 1 July 2018 manuscripts submitted to ICMJE journals that report the results of clinical trials must contain a data sharing statement”<sup>551</sup> and (2) [c]linical trials that begin enrolling participants on or after 1 January 2019 must include a data sharing plan in the trial’s registration.”<sup>552</sup> The abovementioned “sharing statements” must specify: whether individual de-identified participant data (including data dictionaries) will be shared; what data, in particular, will be shared; whether additional, related documents will be available (e.g., study protocol, statistical analysis plan, etc.); when the data will become available and for how long; by which access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). The fact that editors may take data sharing statements into consideration when making editorial decisions could trigger a mechanism similar to that of the 2004 ICMJE’s decision, representing yet a new example of powerful interaction between the WHO’s goals and the directive of the scientific community.

While it seems premature to draw observations on the matter, it seems clear that assessing the data-sharing issue will (i) once again entail an exercise in balancing the interests of subjects in the protection of their privacy as well as in access to transparent clinical trials, the interests of the industry in the control over the data potentially relevant for the development of new products as well as in lowering the administrative burden, and the interests of the investigators’ community in having access to updated data as well as in lowering the risk of selective publication. And (ii) in any event, it once again represents an attempt to tackle a concern (the attempt towards a responsible data-sharing of clinical trials results) that is global and that cannot be effectively regulated without a common international effort.

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<sup>549</sup> Taichman, Darren B., et al. “Data Sharing Statements for Clinical Trials—A Requirement of the International Committee of Medical Journal Editors.” (2017): 2277-2279.

<sup>550</sup> *Ibid.*

<sup>551</sup> *Ibid.*

<sup>552</sup> *Ibid.*

## V. Preliminary Conclusions

To conclude, in the context of this contribution, the role and evolution of clinical trial registries represent an interesting issue. This chapter aimed at providing the reader with an overview of the competing interests behind clinical trials registration, with some fundamental information about the evolution and functioning of the most relevant platforms, and identified current challenges and potential policies related to those challenges in the context of clinical trials registration.

Several conclusions can be presented, in terms of both which interests are involved and how to promote and implement change.

First, the existence of clinical trials registries and in particular of the ICTRP serves as evidence that there is global interest in the regulation of clinical trials, as well as the need for concrete compliance instruments to achieve uniform and permanent results.

Second, the dynamic functioning of the registries shows that such regulation can be implemented positively by relying on the interaction between institutions and the clinical trials community (*in primis*, representatives of the scientific community such as the ICMJE's).

Third, it confirms that the interests of several stakeholders are aligned on the issue of access, that the trend of increased access is still peaking, and that in the next months it will potentially focus on the issue of mandatory data sharing.

## **CHAPTER SEVEN: PRACTICAL ANALYSIS OF CLINICAL TRIALS' DYNAMICS**

### I. Introduction

This chapter aims at elaborating some considerations that regard the international dimension of clinical trials relying on a “practical” approach. In particular, the two main goals of this contribution are the presentation of some opinions collected from clinical trials stakeholders and the collection and discussion of recruitment-related data. In particular, sub-sections II to V in this chapter present the results of interviews conducted with clinical trials sponsors, patients' and consumer organizations, and investigators. Despite the lack of statistical value of the results, the interviews contribute to clarifying the approach and position of the main clinical trials' stakeholders with regard to the

current dimension and regulatory challenges of clinical trials. Sub-section VI introduces the findings of a simple empirical analysis conducted on the basis of a sample of 394 clinical trials, and presents some observations that can be drawn from the analysis of such data.

## *II. Sponsors*

The first survey elaborated aimed at collecting information and opinions from a sample of representatives in the category of sponsors i.e. the subjects – sometimes public, often private – that traditionally organize and/or finance clinical trials (or some portions of clinical trials). The first step of the research regarded the identification of a sample of sponsors and will be described in sub-section (1). The second step regarded the submission of a list of questions to the sponsors and will be described in sub-section (2). Finally, sub-section (3) will introduce some preliminary findings.

### *(1) Presentation of the Sample*

In order to identify potential interlocutors to collect the sponsors' opinion on current clinical trial-related challenges, a sample of sponsors to be contacted was identified. In order to ensure an accurate yet randomized selection, the following steps were taken.

First, access to an international database commonly utilized for networking purposes by the pharmaceutical sector was obtained. The database lists activity and contact information for more than 47.000 companies (including companies active in sectors such as biotechnology, pharmaceutical, medical technology, investors, professional services and consulting, public and non-profit organizations, health tech, etc.). Its search system allows for tailored research on the basis of the sector of industry in which sponsors are active, of the area of the world/country in which they are based, and on the basis of keywords. By combining keywords and selecting either a specific industry sector or area of the world, it is possible to obtain a set of results that are impartially identified by the database.

Second, several searches were run in the database with the objective of obtaining a useful sample of contacts. All the searches were run on the same day to avoid variability due to changes in the database's content and/or functioning. The first set of searches used the keywords "clinical trials" for five sub-categories of sponsors (divided on the basis of the area of activity): biotechnology – therapeutics and diagnostics, biotechnology – research

and development services, pharmaceutical, medical technology, and public and non-profit organizations. Five searches were run, each one selecting one sub-category and using the keywords “clinical trials.”<sup>553</sup> The first five results of each search were extracted. Hence, a pool of 25 sponsors was obtained, each of them representing a company/institution active in one of the five sub-categories and specialized in clinical trial related activities. The second set of searches used the keywords “clinical trials” for seven sub-categories of sponsors (divided on the basis of their geographic location): Africa, Asia, Europe, Central America, Oceania, South America, US and Canada. Seven searches were run, each one selecting one sub-category and using the keywords “clinical trials.”<sup>554</sup> The first five results of each search were extracted. Hence, a pool of 35 sponsors was obtained, each of them representing a company/institution active in one of the seven geographic areas and specialized in clinical trials related activities. Of the 60 contacts obtained, 10 were removed due to overlapping.<sup>555</sup>

Third, the 50 sponsors identified were contacted. Each of them was asked to participate in a research regarding the regulatory challenges in the clinical trials sector. Four of them agreed to be interviewed.<sup>556</sup> Their answers were collected within a six-day span. Preliminarily, it can be noted that the four companies/institutions that agreed to participate in the research are based in the UK, Taiwan, Belgium, and in the US respectively.

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<sup>553</sup> Therefore, the five searched run were the following: (search 1a) “clinical trials” within the sub-category of sponsors active in the “biotechnology – therapeutics and diagnostics” sector, (search 2a) “clinical trials” within the sub-category of sponsors active in the “biotechnology – research and development services” sector, (search 3a) “clinical trials” within the sub-category of sponsors active in the “pharmaceutical” sector, (search 4a) “clinical trials” within the sub-category of sponsors active in the “medical technology” sector, (search 5a) “clinical trials” within the sub-category of sponsors active in the “public and non-profit organizations” sector.

<sup>554</sup> Therefore, the five searched run were the following: (search 1b) “clinical trials” within the sub-category of sponsors active in Africa, (search 2b) “clinical trials” within the sub-category of sponsors active in Asia, (search 3b) “clinical trials” within the sub-category of sponsors active in Europe, (search 4b) “clinical trials” within the sub-category of sponsors active in Central America, (search 5b) “clinical trials” within the sub-category of sponsors active in Oceania, (search 6b) “clinical trials” within the sub-category of sponsors active in South America, (search 7b) “clinical trials” within the sub-category of sponsors active in the US and Canada.

<sup>555</sup> Substantially, the 10 contacts would have represented a duplication of the same results. They represent companies/institutions that are e.g. among the first five results in search 1a as well as among the first five results in search 1b.

<sup>556</sup> The results were registered using online forms. Anonymity was guaranteed to participants.

## *(2) Presentation of the Survey*

Each of the four sponsors that agreed to participate in the survey received a list of 13 questions. For some questions, sponsors were asked to select one answer among an available set of alternatives. In any event, they were given the possibility to clarify their answers adding further comments. Table 4 lists the topics addressed by each main question (and a set of sub-questions).<sup>557</sup>

The first eight questions had the objective of clarifying the nature and size of the activity of each company/institution. The last two questions aimed at collecting the opinion of the sponsors on the regulation of clinical trials.

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Table 4  
Survey Submitted to Clinical Trials Sponsors  
(Topics addressed by each question)

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Question 1	Name of the company/institution, name of the subject representing it, country in which the company/institution is based.
Question 2	Main field in which the company/institution is active.
Question 3	Clinical trials' phases in which the company/institutions involved.
Question 4	Amount of clinical trials in with the company/institution is involved (on a yearly basis).
Question 5	Countries in which the company/institution operates in the clinical trials field (sub-issues: percentage of their clinical trials conducted "abroad" and size of such trials, in terms of how many countries they involve).
Question 6	Recruitment practices used by the company "abroad" (especially with regard to reliance on local recruiters).
Question 7	Involvement of the company/institution in the transfer of foreign-obtained data in their country.
Question 8	Main focus of the company (i.e. on quality increment, access increment, or cost reduction).
Question 9	Opinion on the current level of regulation of clinical trials through legislation.
Question 10	Opinion on the benefit/challenges connected with the implementation of a binding international (i.e. "universal") regulation of clinical trials.

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## *(3) Results*

Given that the sample of interviewed companies/institutions encompasses only four subjects, the results of the survey here presented do not have statistical value. However,

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<sup>557</sup> The topics listed in the table are 10, given that two of the 13 original questions are subsidiary to other main questions and one of the 13 original questions allowed participants to add further comments, if they wanted to.

given that the subjects interviewed represent major stakeholders, their input could still be deemed interesting to the extent that they help clarify the position of the “average sponsor” with regard to the size of the activities conducted and clinical trial regulation.

As to the activity conducted by each sponsor, its size, and its international nature as stated above, the four companies/institutions that agreed to participate in the research are based respectively in the UK, Taiwan, Belgium, and in the US. The sectors in which they are active are respectively the supply of investigational medicinal products for clinical trials, the general organization and carrying out of clinical trials, clinical trials’ monitoring, and a broad range of pharmaceutical research and development activities. Three of the four sponsors are involved in clinical trials from phase I to IV, one is only involved in phase III studies. On average, they are involved in more than 15 clinical trials per year. They are all involved in clinical trials that take place in more than one country – but the extent to which their activity is of international nature varies: the most “international” of the sponsors conducts 90% of its clinical trials in approximately 10 countries.<sup>558</sup> Three of the four sponsors are involved in recruitment procedures that take place “abroad” and two of them consider them “complex enough to require the cooperation of third-party recruiters” on-site. As to the import of foreign clinical data (i.e. obtained through clinical trials conducted “abroad”), the role of the four sponsors varies significantly, with only one of them regularly involved in such activity. This first set of results supports the finding that the four interviewed sponsors represent companies/institutions involved in a variety of activities, the factors rendering them similar being the fact that they all participate in clinical trials with an international dimension.

As to their opinion on current clinical trials regulatory standards, it is interesting to note that the answers given on this topic are almost identical. First, they all consider quality to be the pivotal concept in the field of clinical trials, even *vis a vis* the needs for increased access and reduction of costs. Second, they all consider the field of clinical trials to be “regulated at a correct level” (hence, currently neither over- nor under regulated).<sup>559</sup> Third, when asked to express their position on the opportunity of implementing a detailed

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<sup>558</sup> As of the other sponsors: one declined to answer to the question, one declared that 30% of the clinical trials in which it is involved take place in at least five countries, another declared that 48% of the clinical trials in which it is involved take place in two countries.

<sup>559</sup> However, it is worth noting that the level of regulation of the field of clinical trials varies in the areas in which the four different sponsors are active.

binding international regulation of clinical trials, on a 7-point Likert scale,<sup>560</sup> the sponsors replied with opinions varying from point three and point seven in the scale.<sup>561</sup> Three sponsors out of four consider the opportunity to implement such legislation more beneficial than not. Interestingly, the sponsors that expressed a relatively less favorable opinion on the benefits of implementing an international regulation are those based in Taiwan and Belgium. It can be hypothesized that the reason for which two of the sponsors expressed a relatively more positive opinion about the issue lies not necessarily in their geographic location, but on the extent to which those two companies/institutions operate internationally. In fact, the two sponsors that voted more favorably on the issue are also the two that conduct the largest number of clinical trials “abroad.”

To conclude, two observations can be derived from this portion of research. First, all four sponsors interviewed – while engaged in different kinds of activities and based in different areas of the world – are active at the international level, confirming that even for the small sample here studied clinical trials have an international dimension. Second, none of the interviewed sponsors completely denied the fact that implementing a binding international (i.e. “universal”) regulation of clinical trials could be associated with some benefits; however, the extent to which the four sponsors associate such legislation with benefits varies.

### III. Human Subjects

The second survey elaborated aimed at collecting information and opinions from a sample of representatives of patients’ organizations. The main reason for contacting such organizations is that they can be seen as giving voice to the concerns and opinions of patients i.e. human subjects that either take part in clinical trials or may have the prospect of doing so. The first step of the research regarded the identification of a sample of patients’ organizations and will be briefly described in sub-section (1). The second step regarded the submission of a list of questions to the organizations and will be described in sub-section (2). Finally, sub-section (3) will introduce some preliminary findings.

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<sup>560</sup> The scale provided the possibility to express an opinion from one (not beneficial at all) to seven (absolutely beneficial).

<sup>561</sup> Specifically, they picked point-three, point-five, point-six, and point-seven on the scale.

### *(1) Presentation of the Sample*

The primary intention of this study was to pool patients' organizations at the international (global) level. With this goal, several ways of identifying and randomly selecting organizations to be contacted were assessed. Due to the lack of an international database of such organizations, however, it was deemed appropriate to restrict the sample of organizations to be contacted to the those identified at the level of the EU Registry of Clinical Trials.<sup>562</sup> The list encompasses European branches of international patients' organizations or international organizations themselves when a European branch does not exist. Second, contact points for each organization were researched.<sup>563</sup> Third, as a result, 33 organizations were successfully contacted. Each of them was asked to participate in research regarding the regulatory challenges in the clinical trials sector. Four of them agreed to be interviewed.<sup>564</sup> Their answers were collected in a 20 day span.

### *(2) Presentation of the Survey*

Each of the four organizations that agreed to participate in the survey received a list of 12 questions.<sup>565</sup> For some questions, they were asked to select one answer among an available set of alternatives. In any event, they were given the possibility to clarify their answers by adding further comments.

The first eight questions had the objective of clarifying the nature and size of the activity of each organization. The last two questions aimed at collecting the opinion of the organizations on the regulation of clinical trials. Table 5 lists the topics addressed by each main question (and set of sub-questions).

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Table 5

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<sup>562</sup> A list of the EU Clinical Trials Register – “Patients’ and Consumers’ Organisations’ Contact Information” list is available at “News update.” *EU Clinical Trials Register - Update*, [www.clinicaltrialsregister.eu/](http://www.clinicaltrialsregister.eu/).

<sup>563</sup> This step was necessary due to the fact that the list provided on the EU Clinical Trial Register includes only links to the organizations’ websites. Furthermore, note that the EU Clinical Trial Register provides users also with a list of “Healthcare Professionals’ Organisations contact information.” The list is available at “News update.” *EU Clinical Trials Register - Update*, [www.clinicaltrialsregister.eu/](http://www.clinicaltrialsregister.eu/). For each of the organization in that list a contact point was identified and 27 organizations were effectively reached. However, none of them agreed to participate in a survey/interview for the purpose of this research.

<sup>564</sup> The results were registered using online forms. Anonymity was guaranteed to participants.

<sup>565</sup> The topics listed in the table are 10 given that one of the 12 original questions is subsidiary to other main questions and one of the 12 original questions allowed participants to add further comments, if they wanted to.

Survey Submitted to Clinical Trials Sponsors (Topics addressed by each question)	
Question 1	Name of the organization, name of the subject representing it.
Question 2	Main field in which the company/institution is active.
Question 3	Clinical trials' phases in which the organization's members are involved.
Question 4	Amount of clinical trials in with the organization is involved (on a yearly basis).
Question 5	Countries in which the organization operates in the clinical trials field (sub-issues: percentage of those clinical trials that are conducted at the international level).
Question 6	Opinion of the organization on the recruitment practices used for clinical trials.
Question 7	Involvement of the organization in the transfer of foreign-obtained data in their country.
Question 8	Main focus of the organization (i.e. on quality increment, access increment, or cost reduction).
Question 9	Opinion on the current level of regulation of clinical trials through legislation.
Question 10	Opinion on the benefit/challenges connected with the implementation of a binding international (i.e. "universal") regulation of clinical trials.

### (3) Results

As in the case of the survey addressed to sponsors described in the previous section of this chapter, research that entails interviews from only four patients' organizations does not allow for results that are statistically relevant. Nevertheless, given that the subjects interviewed represent major stakeholders, their input could still be deemed interesting to the extent that they help clarify the position of some patients' organizations with regard to the size of the activities conducted and clinical trial regulation.

Each of the four organizations that agreed to take part in this research represents patients affected by a specific condition. Their main goal varies from improving the quality of life of people affected by a certain condition (which was listed by three of the four organizations), to providing "a framework for all members to work collaboratively in order to accelerate research pathways"<sup>566</sup> related to that specific condition (which was listed by three of the four organizations), to connecting healthcare professionals and researchers interested in the condition and to e.g. support their applications for research grants (which was listed by one of the four organizations). Three of the organizations

<sup>566</sup> This wording was specifically used by one of the organizations sampled but similar declarations were made also by the other three organizations.

declared to be active (directly or through their members) in phases I to IV of clinical trials, one limits its focus to phases III and IV. All four organizations or their members are involved in clinical trials that take place in more than one country.<sup>567</sup> When asked more information about how many of the clinical trials they deal with are international and how many countries they tend to involve, all four organizations declared that 100% of the clinical trials that they deal with are international and involve on average four countries (in the case of two organizations) and 10 countries (in the case of one organization).<sup>568</sup> As to their position on recruitment challenges, two organizations pointed out that their members are directly involved in the recruitment of participants in clinical trials.<sup>569</sup> Only one organization is involved in issues regarding the import of data obtained in one country to a different one – and the involvement is “rare.” Two of the organizations find that the quality of clinical trials is the pivotal value for their action, two found that access of as many subjects as possible to clinical trials is the pivotal value for their action.

With regard to the opinion expressed by the four organizations on the current clinical trials regulations, it can be noted that two organizations labeled the clinical trials field as over-regulated; one organization labeled it as regulated at a correct level; and one defined it as “not correctly regulated.”<sup>570</sup> Furthermore, when asked to express their position on the opportunity of implementing a detailed binding international regulation of clinical trials, on a 7-point Likert scale,<sup>571</sup> one organization declined to answer the question while the other three responded in various ways.<sup>572</sup> Interestingly, the organization that finds the

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<sup>567</sup> Specifically, three of the four organizations are interested/active in clinical trials that take place in more than one EU country (but not non-EU countries) while one organization is interested/active in clinical trials that take place in more than one country in general, including non-EU countries.

<sup>568</sup> One of the organizations could not precisely provide information about the average number of countries involved.

<sup>569</sup> Of the other two organizations, one does not deal with the recruitment-stage in clinical trials and the other outsources recruitment-efforts to a third party, due to the complexity of the matter. In general, it can be noted that two of the four organizations (independently from whether they directly deal with recruitment or not), agreed to disclose the countries in which they are familiar with recruitment policies and support physicians and patients: for one organizations such counties are France, Germany, and Italy; for another organization they are Australia, the UK, and the US.

<sup>570</sup> In particular, the organization finds that the main that is not correctly regulated is the one of endpoint(s)-identification.

<sup>571</sup> The scale provided the possibility to express an opinion from one (not beneficial at all) to seven (absolutely beneficial).

<sup>572</sup> Specifically, they picked point-three, point-six, and point-seven on the scale.

introduction of such a regulation international binding relatively less beneficial than the other two, nevertheless pointed out that excessive variations between standards applicable in different countries exist and that this variations may “hinder clinical trials taking place in some countries.”

To conclude, on the one hand, similarly to that observed in the case of the sponsors, also in the case of patients’ organizations it can be noted that the dimension of clinical trials has regularly reached an international scale. However, this may be due to the fact that the organizations pooled are mainly active at the European supra-national level or at the international level. On the other hand, it can be noted that none of the four organizations considers the field of clinical trials to be under-regulated – this, of course, may be due to the fact that they are active at the European level, where legislation on clinical trials is relatively stringent.

#### IV. Investigators

The third surveys elaborated within this research aimed at collecting input from investigators, the third category primarily involved in clinical trials, together with sponsors and human subjects. The first step of the research regarded the identification of a sample of investigators and will be briefly described in sub-section (1). The second step regarded the submission of a list of questions to the investigators and will be described in sub-section (2). Finally, sub-section (3) will introduce some preliminary findings.

##### *(1) Presentation of the Sample*

In order to obtain a pool of contacts of investigators that could participate in the survey, the main source was identified as the ICTRP. In fact, its “advanced search” function allows the observation of clinical trials registered and recruiting in a multitude of countries in chronological order.<sup>573</sup> Therefore, first of all, a set of countries was selected. 53 countries were randomly selected starting from the “Country Classification” section included in the United Nations World Economic Situation and Prospects for year 2017.<sup>574</sup> Second, for each of the countries a search on the ICTRP was conducted within a two

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<sup>573</sup> *ICTRP Search Portal Advanced Search*, [apps.who.int/trialsearch/AdvSearch.aspx](https://apps.who.int/trialsearch/AdvSearch.aspx).

<sup>574</sup> UN, *World Economic Situation and Prospects 2017* (New York, 2017) 153-154. Note that the main reason for which this list was used is that it provides for a distinction between developed economies, economies in transition, and developing economies. Such distinction will be considered the relevant one in Section VI in this Chapter.

week span. The three variables used were the selection of phase I to VI of clinical trials, the selection of the country, and the date of registration. For every country, the first 10 results (which are displayed in chronological order- the most recently registered clinical trials being displayed first) were taken into consideration with the exception of cases in which some of the 10 first clinical trials displayed among the results did not provide for the email contact of an investigator (in this case, results after the first 10 were taken into consideration in order to nevertheless obtain a sample of 10 clinical trials).<sup>575</sup> Table 6 displays the clinical trials that were sampled on the basis of the countries of recruitment. Third, as a result, 424 clinical trials (and investigators' contacts for each of them) were identified. Each of them was contacted and 15 investigators agreed to participate in the survey presented here.<sup>576</sup> Preliminarily, it can be noted that 10 investigators are based in developed economies and five are based in developing economies or economies in transition.<sup>577</sup>

Country	N° Clinical Trials Sampled
Afghanistan	4
Albania	6
Algeria	10
Angola	2
Argentina	10
Armenia	5
Australia	9
Bahrain	7
Belgium	10
Belize	1
Benin	4
Bolivia	7
Bosnia and Herzegovina	10
Bulgaria	10
Burundi	1

<sup>575</sup> Note that in the case of four countries (Australia, China, Italy, and India) the final sample taken into consideration encompassed 9 clinical trials, despite the potential availability of 10 results. This choice is the consequence of the fact that in those four cases the contacted investigators communicated that their study was no longer recruiting.

<sup>576</sup> The results were registered using online forms. Anonymity was guaranteed to participants.

<sup>577</sup> The distinction between such categories is based on UN, *World Economic Situation and Prospects 2017* (New York, 2017) 153-154.

Burundi	1
Cameroon	9
Canada	10
Chad	1
Chile	10
China	9
Croatia	10
Denmark	10
Dominican Republic	10
France	10
Germany	10
Ghana	8
Guatemala	10
Iceland	10
India	9
Israel	10
Italy	9
Japan	10
Kenya	10
Malaysia	10
Morocco	10
Namibia	2
Netherlands	10
New Zealand	10
Nigeria	10
Pakistan	10
Qatar	10
Romania	10
Russian Federation	10
Senegal	2
Serbia	10
Switzerland	10
Thailand	10
The Bahamas	1
Ukraine	10
United Kingdom	10
United States	10
Uruguay	7

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## (2) Presentation of the Surveys

Each of the 15 investigators that agreed to participate in the survey received a list of 11 questions.<sup>578</sup> For some questions, they were asked to select one answer among an available set of alternatives. In any event, they were given the possibility to clarify their answers by adding further comments. The first set questions had the objective of clarifying the nature and size of the activity of each investigator. The second set of questions aimed at collecting the opinion of the investigators on the regulation of clinical trials. Table 7 lists the topics addressed by each main question (and set of sub-questions).

Question 1	Name of the investigator and affiliation (with a company/institution)
Question 2	Main field in which the company/institution is active.
Question 3	Clinical trials' phases in which the investigator involved.
Question 4	Location of the investigator's work, of her sponsor, and of the human subjects taking part in her clinical trial.
Question 5	Possible reasons for which the investigator was selected by a specific sponsor.
Question 6	Familiarity of the investigator with clinical trials' registration.
Question 7	Main focus of the investigator (i.e. on quality increment, access increment, or cost reduction).
Question 8	Opinion on the current level of regulation of clinical trials through legislation.
Question 9	Opinion on the benefit/challenges connected with the implementation of a binding international (i.e. "universal") regulation of clinical trials.

A few further methodological considerations are worth noting.

(i) The questions were divided in two separate surveys, one addressed to investigators based in developed economies and one for investigators based in developing economies or economies in transition.<sup>579</sup> The rationale behind the submission of two separate surveys was the willingness to preserve the ability to distinguish participants on the basis of the countries in which they are active. However, the division of investigators in two

<sup>578</sup> The topics listed in the table are 9 given that one of the 11 original questions are subsidiary to other main questions and one of the 11 original questions allowed participants to add further comments, if they wanted to.

<sup>579</sup> Note that the term "based" in this context technically means "associated as contact point with a "clinical trial recruiting in a developed economy/developed economy/economy in transition."

groups *a priori* (investigators based in developed economies and investigators based in developing economies or economies in transition – to which two different surveys were sent) proved to be an ineffective strategy.<sup>580</sup> Therefore, the results presented here are organized on the basis of a division within the same two groups but made *a posteriori*.<sup>581</sup> This choice is not expected to produce any effect on the quality of the results presented, given that the questions included in the surveys are substantially identical.<sup>582</sup> This methodological choice is nevertheless disclosed in the interest of transparency.

(ii) Due to the same circumstances discussed in the first methodological note, it was possible for an investigator based in Peru to take part in the survey, despite that fact that Peru was not one of the sampled countries. The investigator was necessarily listed as a contact point for a clinical trial taking place in more than one country i.e. Peru, and one of the countries sampled within this research (listed in Table 6). This circumstance is arguably not capable of affecting the reliability or relevance of the answers provided by the investigator.

(iii) One investigator among those contacted agreed to participate in the research but provided answers that did not appear to be reliable and were therefore discarded.

To conclude, none of the methodological notes are deemed capable of affecting the results presented. Nevertheless, they were disclosed in the interest of transparency.

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<sup>580</sup> The main reason depends on the fact that investigators serving as contact points for clinical trials recruiting in a multitude of countries appear as contact point for clinical trials identified by this research as belonging to the sample for one country but may be practically based in another country. For example, in the case of a clinical trial with a main investigator in the US, but which recruits participants both in Kenya and the US, the contact point available on the ICTRP may be a US-based investigator or a Kenya-based investigator and appear both among the results of the search run for clinical trials recruiting in the US and in Kenya. Therefore, until the submission of the answers submitted by that investigator to the survey presented in this contribution it would have not necessarily be possible to predict whether the contact point is based in the US or in Kenya.

<sup>581</sup> Following the division *a priori*, nine investigators filled the survey sent to investigators which served as contact points for clinical trials that were recruiting – among others – in developed economies and seven filled the survey sent to investigators which served as contact points for clinical trials that were recruiting – among others – in developing economies or economies in transition. *A posteriori*, ten of the participant investigators are based in developed economies and 6 are based in developing economies or economies in transition. The latter division will be the one taken into consideration from now on in this contribution.

<sup>582</sup> Question 5 listed in Table 7 is the only question that differs in the two surveys, given that participants were given more options to pick from to respond when they received the survey addressed to investigators based in developing economies or economies in transition.

### *(3) Results*

As in the case of the surveys addressed to sponsors and patients' organizations described in the previous sections of this chapter, a research entails interviews of only 15 investigators does not allow for results that are statistically relevant. Nevertheless, given that the subjects interviewed represent major stakeholders, their input could still be deemed interesting to the extent that they help to clarify the position of some investigators with regard to the size of the activities conducted and clinical trial regulation.

As noted above, ten of the participant investigators are based in developed economies<sup>583</sup> and 5 are based in developing economies or economies in transition.<sup>584</sup>

Ten investigators are employed by Universities, two work for a publicly funded governmental agency which engages in clinical research, two for a private company, and one for a mixed private-public research center. Five are involved in clinical trials from Phase I to IV, the other ten are involved in only one phase (the prevalent being Phase III, with four investigators working only on Phase III clinical trials) or a combination of two or three phases.

As to the relationship with sponsors, only one investigator declared to operate without a sponsor (being a sponsor-investigator); nine investigators rely on a sponsor based in their own country, one relies on a sponsor based in a different country but on the same continent, four rely on sponsors based in different continents.<sup>585</sup> When asked why the sponsor may have chosen to finance a clinical trial conducted on a different continent, the four investigators provided a variety of reasons: all four listed the good quality of the result generated, one (based in Switzerland) explained that the sponsor is planning to commercialize the tested treatment in the country in which the clinical trial is conducted; the two investigators based in developing economies or economies in transition

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<sup>583</sup> Austria, Belgium, Denmark, Italy, New Zealand, Switzerland, the Netherlands (two different investigators, for two different clinical trials), and the United Kingdom (two different investigators, for two different clinical trials).

<sup>584</sup> Nigeria, Peru, Russia (two different investigators, for two different clinical trials), and Serbia.

<sup>585</sup> In particular, the four investigators conducting clinical trials sponsored by an actor based in a different continent are based in New Zealand, Peru, Russia, and Switzerland.

(respectively Peru and Russia) referred both to “good availability of participants” as the reason for being chosen by the foreign-based sponsor.<sup>586</sup>

With regard to human subjects, 12 investigators declared that their work focuses on participants based in their same country; three declared that their participants in clinical trials are based on a different continent.<sup>587</sup> Furthermore, 11 investigators identified the quality of clinical trials as the pivotal value for their work, two identified access of as many subjects as possible to clinical trials as the pivotal value, and only one (based in Serbia) identified convenient costs as pivotal value for her work.<sup>588</sup>

When asked to clarify why the clinical trial (or trials) that they are involved in is currently registered in a clinical trial registry, investigators replied listing a variety of reasons in different combinations. 13 investigators listed “to comply with requirements set by the scientific community (e.g. in order to publish the study)” as one of the reasons – among those, nine listed such motivation as the *only* motivation supporting their decision to register the clinical trial; six declared that one motivation was the need to comply with national legislation – among those, two listed such motivation as the *only* motivation supporting their decision to register the clinical trial; three did it to comply with requirements set by their sponsor.

When asked to express their opinion on the current regulatory standards applicable to clinical trials, 11 investigators declared that, in their opinion, the clinical trials field is currently regulated at the correct level;<sup>589</sup> four investigators defined the field of clinical trials as being “over-regulated.” When asked how beneficial they would consider the implementation of a detailed binding (“universal”) regulation at the international level

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<sup>586</sup> Notably, none of the two investigators listed “relatively low costs” or “relatively low administrative burden” as the reason for being chosen by a foreign-based sponsor.

<sup>587</sup> The three investigators are based in Austria (one) and in the United Kingdom (two).

<sup>588</sup> One investigator chose not to pick a single option and declared that “the optimal balance between cost and quality” it’s the pivotal value for her work.

<sup>589</sup> One of them, however, specified that despite the correct level of regulation, guidance on how to apply the law in the field of clinical trials is still insufficient. Interestingly, when asked to clarify her position, the investigator explained that “an international regulation of CTs could be really hard to implement in practice as countries can vary so much internationally. Having a solid harmonized approach to GCP is already in place but would be helpful if regulators such as the EMA and FDA could be clearer in how the regulations and ICH GCP can be implemented in practice (generally they only publish non-binding guidance).”

on a 7-point Likert scale,<sup>590</sup> the 15 investigators replied in a variety of ways. On average, they picked point-4 on the scale.<sup>591</sup> Despite the fact that the sample does not allow for statistically relevant results, it can be noted that, within the sample, investigators based in developed economies labeled the implementation of such a regulation as more beneficial than investigators based in developing economies and economies in transition.<sup>592</sup>

To conclude, three observations can be made in the light of the obtained results. First, it can be noted that a prevalent international dimension of clinical trials was not present in the operation of the investigators that participated in the research presented, neither with regard to the relationship between sponsors and investigators, nor with regard to that between investigators and human subjects. Second, interesting opinions emerged in the context of compliance with registration requirements, confirming that the main reason for which investigators recur to clinical trial registries is the underlying interest in publishing their study, rather than the need to comply with legal provisions. Finally, third, among investigators, there is no absolutely positive opinion on the benefits associated with implementing an international binding clinical trials regulation; also, the association of such an idea as being beneficial is more pervasive among sponsors based in developing economies; while it is not possible to clearly identify a reason for such divergence, one of the possible explanations could be because most of the developing countries pooled are EU Member States, and are therefore already used to operating in a context in which harmonization and supra-national regulations are fostered when appropriate; on the other hand, investigators based in developing countries or economies in transition may see the need to comply with western-originated standards as more burdensome (and, potentially, as affecting their capability of attract foreign-based sponsors).

#### V. Clinical Trials' Globalization

The research conducted to collect investigators' contacts described above had a secondary aim: collecting up-to-date information on the dimension of clinical trials. The hypothesis with which this portion of research was approached is multifaceted: (a) to test

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<sup>590</sup> The scale provided the possibility to express an opinion from one (not beneficial at all) to seven (absolutely beneficial).

<sup>591</sup> Precisely, 3.9.

<sup>592</sup> In particular, on average, investigators based in developed economies picked point 4,4 on the scale and investigators based in developing economies and economies in transition picked point 3 on the scale.

to which extent clinical trials have “gone global,” (b) to assess whether some countries are more affected by such globalization than others, and (c) to estimate whether there is a correlation between the extent to which clinical trials conducted in countries are “international” in size, and their economic status (i.e. developed economies, developing economies or economies in transition).

### *(1) Presentation of the Sample*

The sample utilized in this portion of research is the same used to contact investigators described above. The only data eliminated in this portion of research is data regarding countries in which less than ten clinical trials registered as recruiting in the ICTRP were present. This decision was rendered necessary in order to ensure a more uniform sample.<sup>593</sup> As a result, 41 countries were taken into consideration. One further piece of information was retrieved for each clinical trial taken into consideration, in addition to that described in the section dedicated to the presentation of the sample for the investigators’ survey. In fact, for each of the clinical trials taken into consideration, the number of countries in which such clinical trial was recruiting was retrieved. The ICTRP makes this possible, given that the individual page dedicated to each clinical trial registered lists the countries in which the trial is recruiting.

The data collected is presented in Table 8. In the table, the first column includes the name of each country taken into consideration; the second column clarifies whether the country is deemed a developed economy or developing/in transition;<sup>594</sup> the third column displays how many clinical trials recruiting in each specific country were sampled;<sup>595</sup> the fourth

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<sup>593</sup> The main concern being the one related to clinical trials of considerable dimension that would have weighted relatively more in the case of countries in which a limited number of clinical trials is conducted. E.g. only one clinical trial recruiting in the Bahamas was registered in the ICTRP at the time in which data was collected. Such clinical trial was recruiting in 196 countries in total. Keeping only this data-point into consideration, the Bahamas would have appeared as a country with 100% clinical trials taking place on its territory being international in nature. To avoid relying on single (or relatively small) data-points, only countries with seven to 10 (or more) registered recruiting clinical trials were taken into consideration.

<sup>594</sup> The distinction between such categories is based on United Nations, *World Economic Situation and Prospects 2017* (New York, 2017) 153-154.

<sup>595</sup> The initial goal was to sample 10 clinical trials per country, but (i) as noted above, in the case of four countries (Australia, China, Italy, and India) the final sample take into consideration encompassed 9 clinical trials, despite the potential availability of 10 results. This choice is the consequence of the fact that in those four cases the contacted investigators communicated that her study was no longer recruiting. And (ii) in the case of countries with less than 10 recruiting clinical trials registered in the ICTRP a minimum of seven clinical trials were taken into consideration. It is worth noting that the same clinical trial may have been taken into consideration multiple times. This would be the case, for example, of a trial recruiting simultaneously in Germany and Italy. Necessarily, it would represent one of the 10

column displays in how many countries clinical trials that are recruiting in each country recruit on average. Countries in the table are ordered on the basis of the fourth column. The last column is the core data obtained by this portion of research. In order to better explain what the figures included in it represent, an example can be provided, taking into consideration the case of Chile. The following steps were taken: (pre-i) Chile was identified as one of the countries to be taken into consideration i.e. randomly picked from a comprehensive list of countries.<sup>596</sup> (i) On the ICTRP “advanced search” page,<sup>597</sup> a search was run picking Phases I to VI and Chile. (ii) The first ten results (i.e. clinical trials recruiting in Chile) were taken into consideration. (iii) For each of the clinical trials, the information regarding the countries of recruitment was retrieved. A list of countries of recruitment is provided on the ICTRP, and the number of countries for each clinical trial was counted. (iv) The number of countries of recruitment identified for each of the ten clinical trials were summed up (i.e. 129 in the case of Chile) and then divided by the number of clinical trials sampled for Chile (i.e. 10). The result obtained (i.e. 12,9 in the case of Chile) signifies that on average, on the basis of the analyzed sample, clinical trials that recruit participants in Chile recruit participants also in 11,9 other countries.

Country	Developed or Developing/in Transition	N° Clinical Trials Sampled	N° Recruitment Countries (average)
Iceland	Developed	10	39,5
Bahrain	Developing/Tr.	7	35,1
Algeria	Developing/Tr.	10	34,9
Bulgaria	Developed	10	33,1
Bosnia and Herzegovina	Developing/Tr.	10	32,0
Bolivia	Developing/Tr.	7	31,1
Morocco	Developing/Tr.	10	29,2
Cameroon	Developing/Tr.	9	27,4
New Zealand	Developed	10	27,3
Uruguay	Developing/Tr.	7	25,7

clinical trials taken into consideration as recruiting in Germany and one of the 10 clinical trials taken into consideration as recruiting in Italy. Multiple presences of the same trial in the pool could not have been eliminated without scarifying randomization and in any event do not seem to pose any risk to the viability of the results obtained.

<sup>596</sup> The one provided in UN, *World Economic Situation and Prospects 2017* (New York, 2017) 153-154.

<sup>597</sup> *ICTRP Search Portal Advanced Search*, apps.who.int/trialsearch/AdvSearch.aspx.

Denmark	Developed	10	21,5
United Kingdom	Developed	10	21,1
Guatemala	Developing/Tr.	10	19,2
Romania	Developed	10	19,2
Croatia	Developed	10	17,5
Argentina	Developing/Tr.	10	15,4
Chile	Developing/Tr.	10	12,9
Malaysia	Developing/Tr.	10	11,8
Israel	Developing/Tr.	10	10,1
Serbia	Developing/Tr.	10	9,8
Dominican Republic	Developing/Tr.	10	9,5
Nigeria	Developing/Tr.	10	9,3
Ukraine	Developing/Tr.	10	8,3
Qatar	Developing/Tr.	10	7,5
Russian Federation	Developing/Tr.	10	5,3
Kenya	Developing/Tr.	10	5,2
Canada	Developed	10	4,3
Germany	Developed	10	4,0
Italy	Developed	9	4,0
Pakistan	Developing/Tr.	10	4,0
Ghana	Developing/Tr.	8	3,4
Australia	Developed	9	3,3
France	Developed	10	3,0
Netherlands	Developed	10	2,9
Switzerland	Developed	10	2,5
Belgium	Developed	10	1,9
United States	Developed	10	1,7
China	Developing/Tr.	9	1,0
India	Developing/Tr.	9	1,0
Japan	Developed	10	1,0
Thailand	Developing/Tr.	10	1,0

## *(2) Results*

The study here presented analyzed the areas of recruitment of 394 clinical trials registered on the ICTRP. The fact that for each of the 41 countries taken into consideration only seven to ten clinical trials were analyzed, renders it difficult to generalize the findings of this research. Simultaneously, the fact that the sample was obtained through the ICTRP limits the applicability of such findings to the field of clinical trials that are not registered.

However, following the hypothesis identified above, some considerations may be presented.

(a) The data displayed in Table 8 confirms that clinical trials have “*gone global*.” In particular, it confirms the basic intuition on which this thesis is based: the field of clinical trials is international in nature. In fact, only four countries out of the 41 countries sampled host on their territory clinical trials that recruit only within national borders.<sup>598</sup> In the case of “closed-system” countries, in any event, the degree to which the system is isolated (i.e. virtually all the clinical trials that take place in a country that recruits solely in that country) or “internationalized” does not provide any indication regarding the level of protection awarded to human subjects recruited in that country. However, the consequence of this finding in terms of regulatory considerations is that the vast majority of countries have an interest in taking into consideration the international dimension of clinical trials.

(b) Some countries are more affected by the globalization of clinical trials more than others. In particular, even among the countries that are not “closed-systems,” a certain degree of *variation* exists. Some countries host clinical trials that recruit in a pool of other countries relatively smaller than others – this results in the countries occupying a position in the bottom part of the list included in Table 8. For example, it can be noted that clinical trials that take place in Switzerland on average recruit in Switzerland and in one other country;<sup>599</sup> simultaneously, clinical trials that take place in Algeria on average recruit in Algeria and in 33 other countries.<sup>600</sup> Countries that host more international clinical trials than others, from the regulatory point of view, may have an increased interest in considering the interaction between their national law and international standards.

(c) The existence of a strong *correlation* between the extent to which clinical trials conducted in countries are “international” in size and their economic status (i.e. developed economies, developing economies or economies in transition) is not supported by the findings of this research. Of the 41 countries taken into consideration, 17 represent developing economies. Ten of those fall to the bottom part of the list included in Table 8, meaning that they have a slight tendency to host clinical trials that recruit in relatively small pools of countries. However, such distribution in the list is not particularly evident and does not allow for the conclusion that there is a correlation between the average size

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<sup>598</sup> The four “closed-system” countries are China, India, Japan, and Thailand.

<sup>599</sup> Precisely, 1,5

<sup>600</sup> Precisely, 33,9

of recruitment pools (in terms of countries) and economic status of countries of recruitment.

#### *VI. Preliminary Conclusions*

To conclude, this chapter aimed at providing some insights regarding the global dimension of clinical trials and the characteristics and positions of some stakeholders. It achieved those goals by presenting a set of “case studies” which assessed the opinion of a small pool of sponsors, patients’ and consumers’ organizations, and investigators; and by extracting and analyzing recruitment-related data obtained through the ICTRP.

While conclusions specific to each section are presented above, a few broad observations deriving from this chapter as a whole can be presented. First, the research conducted through contacts with clinical trial stakeholders (sub-sections II-IV) confirmed that in their action the international dimension is persistently relevant. It also confirms that stakeholders have mixed opinions – often depending on their role and geographic location – regarding the optimal level of regulation of clinical trials and the benefits associated with the implementation of a binding international (i.e. “universal”) regulation of clinical trials. Second, the research conducted on recruitment pools on the basis of data retrieved from the ICTRP by collecting of up-to-date information, confirmed that the international dimension is the prevalent dimension in clinical trials and that the vast majority of countries have a virtual interest in the regulation of clinical trials – or at least the opportunity to take into consideration the international scale of the recruitment activities that they host – in the light of such a “global” phenomenon.



## CONCLUSIONS

This thesis identified some of the risks and opportunities of a globalized clinical research environment, with the aim of providing some insights on how to improve the protection of human subjects in clinical trials. In general, the thesis focused on the global dimension of clinical trials and on their status and challenges in developing economies *vis-à-vis* developed economies; it also analyzed the role that different stakeholders play in the field of clinical trials in light of the need to balance their competing interests. To achieve its goals, it adopted a variety of approaches – especially the descriptive, the comparative, and the empirical. It also borrowed and built upon sources from various areas of literature, including international healthcare law and policy literature, as well as scientific research.

Each chapter attempted to respond to the research questions presented in the introduction. The specific answers to the question (or questions) addressed in the chapters are presented at the conclusion of each chapter, in the form of preliminary conclusions.

Therefore, the conclusions presented in this section will not focus on findings that derive from single chapters taken alone, but rather on the big picture that can be observed through the lenses manufactured in this contribution. They can be presented in the form of four questions, with elements taken from each of this thesis' chapters contributing by providing their respective answers.

(i) The first question regards the rationale behind the regulation of clinical trials: *why should clinical trials be objects of legislation?* Chapter Two provides some tools to support a positive answer to this question. In fact, the regulation of clinical trials is necessary in order to fully respect and implement the right to health and the right to information. In particular, regulating clinical trials means addressing specific issues due to which those rights may be negatively affected. In this context, Chapter Two discusses the challenges and opportunities connected with the issue of sample tailoring, subject recruitment, placebo-controlled clinical trials and standards of care, clinical trial registration – which is also addressed in Chapter Six – and informed consent.

(ii) The second question regards the pushing and pulling forces that confront legislative forces in the field of clinical trials regulation: *which are the interests to be balanced in clinical trials regulation?* To provide an answer to this question, Chapter Three presents a “taxonomy” of clinical trial paradigms and competing interests. It suggests that legislators should take into consideration the interests of three stakeholders – human subjects, sponsors, and investigators – and that those interests can be effectively categorized in the light of three competing paradigms – access, cost, and quality. The categorization of clinical trial related issues in these terms represents an original contribution to clinical trial literature. Moreover, with regard to the action of stakeholders, Chapter Four identifies a series of best practices that private stakeholders may take into consideration to preserve the protection of the highest attainable ethical standards when conducting clinical research.

(iii) The third question regards the issue of allocating competences in the regulation of clinical trials: *at which institutional level should clinical trials be regulated?* A few decades ago, “what eventually came to be called syphilis was known as ‘the Neapolitan disease’ among the French and ‘the French disease’ among Italians. Russians called it ‘the Polish disease’ and the Polish called it ‘the German disease.’”<sup>601</sup> Nowadays, arguably, conditions requiring treatments for which clinical trials are on-going do not stop at national borders – consequently, clinical research is far from adopting a solely national (and nationalist) approach. In this context, the empirical analysis included in Chapter Seven (in particular, sub-section V) confirms that the globalized dimension of clinical trials is currently prevalent. In a nutshell, it finds that the vast majority of the 394 clinical trials sampled in the study recruit in more than one country at the same time and that the vast majority of the 41 countries sampled have a virtual interest in appreciating the international dimension of clinical trials that recruit human subjects in their territory. Furthermore, the conclusions of Chapter Two suggest that the nature of some of the challenges that are prominent in the field of clinical trials – in particular, issues such as local standards of care, registration, and informed consent in international clinical trials – require legislative efforts to be promoted at the international level, given that they touch upon rights that belong to human subjects as such, and are not (or should not be) bound

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<sup>601</sup> “Why do we call it that? Backstories of seven disease names.” *STAT*, 24 Oct. 2017, [www.statnews.com/2017/10/24/etymology-disease-names/](http://www.statnews.com/2017/10/24/etymology-disease-names/).

to national borders. As to the division of competences between the international and national level, Chapter Four suggests steadily introducing the reliance on the principle of subsidiarity in order to fully and effectively implement clinical trial legislation at the most appropriate level of institutional power.

(iv) The fourth question regards the challenges that legislative efforts face, especially if carried out taking into consideration the answer provided to the third question: *how should legislators regulate the globalized field of clinical trials?* The findings of this thesis in this context can be summarized in three indications. First, legislators – being at the national, regional, or international level – should be aware of the nature of the challenges that clinical trials pose, as well as of the interests triggered by clinical trials, not to mention the successful dynamics already developed at the international level. In this sense, Chapter Three and Chapter Seven (sub-sections II-IV, dedicated to the description of the opinions expressed by a pool of stakeholders) confirm that the interests of stakeholders are relevant at any institutional level. Furthermore, Chapter Six sees in the development of the ICTRP an example of successful interaction of the complementary regulatory efforts promoted by public actors and the scientific community. Second, the global nature of clinical trials becomes particularly relevant in the case of legislative efforts regarding multi-regional clinical trials and the import of foreign-obtained data. Hence, Chapter Five presents a comparative analysis of the provisions implemented in the EU and the US with regard to globalized clinical trials. The analysis identifies similarities and differences between the two systems in order to provide both private actors interested in compliance and institutional actors interested in law-reform with an up-to-date comparative analysis. Given that the latter relies on the new EU “Clinical Trials Regulation” – which is soon to enter into force and has not yet been object of extensive contributions in literature – it represents a particularly original analysis within clinical trial literature. It is also complemented by an addendum of the status of the EU “Clinical Trials Regulation” in four Members States that agreed to share some information while this thesis was redacted. Third, globalized clinical trials cannot be regulated without taking into high consideration the need to effectively implement common ethical standards. Therefore, Chapter Four in this thesis provides a concrete hypothesis as to the shape that such standards should assume within clinical trial legislation, taking into consideration the challenges posed by the phenomenon of “outsourcing” clinical trials in developing economies.

To conclude, in the dawn of the 20<sup>th</sup> Century, Joseph Conrad wrote that “[t]he conquest of the earth, which mostly means the taking it away from those who have a different complexion or slightly flatter noses than ourselves, is not a pretty thing when you look into it too much.”<sup>602</sup> In light of the research developed and presented within this thesis, it can be said that the same risk applies to the highly modernized and technical, yet extremely “social” in nature and globalized field of clinical trials. In this context, wise legislative efforts, capable of acknowledging complex dynamics – in terms of interests involved, ethical considerations, and geographical challenges – represent the best tool to cast some light into the heart of clinical trial darkness.

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<sup>602</sup> Conrad, Joseph. *Heart of Darkness* (New York: Bantam Books, 1981), at p. 65.

## ADDITIONAL DOCUMENTS

### (1) Zusammenfassung der Dissertation: Recht und Praxis klinischer Studien: Probandenschutz und globale Dynamiken

Die vorliegende Dissertation beschäftigt sich mit den Auswirkungen klinischer Forschung – genauer, klinischer Studien – bezüglich des Rechts und der Praxis auf internationaler Ebene. Sie identifiziert einige der Risiken und Möglichkeiten eines globalisierten Umfelds klinischer Studien und zielt darauf ab, Einblicke in die Verbesserung des Menschenrechtsschutzes in klinischen Studien zu geben. Allgemein konzentriert sie sich auf die globale Dimension klinischer Studien und ihres Status und die Herausforderungen in Entwicklungsländern *vis a vis* entwickelten Ländern; Sie analysiert darüber hinaus die Rolle, die verschiedene Akteure im Bereich klinischer Studien, hinsichtlich der Notwendigkeit, die konkurrierenden Interessen auszubalancieren, spielen. Um diese Ziele zu erreichen, werden eine Reihe von Ansätzen verfolgt – insbesondere der beschreibende, vergleichende und der empirische Ansatz. Sie baut auf Quellen verschiedener literarischer Bereiche auf (und trägt zu diesen bei), einschließlich des internationalen Gesundheitsrechts, der einschlägigen Literatur sowie wissenschaftlicher Forschung.

Jedes Kapitel versucht, auf spezifische Forschungsfragen einzugehen:

Kapitel Eins stellt eine umfassende Überprüfung der Literatur im Bereich des Rechts und der Praxis klinischer Studien dar, mit einem besonderen Fokus auf deren internationale Dimension. Kapitel Zwei beschreibt die wesentlichen Rechte, die bei der Durchführung von und Teilnahme an klinischen Studien berührt werden. Insbesondere werden das Recht auf Gesundheit sowie das Recht auf Information angesprochen. Kapitel Drei beschreibt Hauptakteure klinischer Studien (teilnehmende Personen, Sponsoren und Forscher) und wie ihre Interessen koordinieren oder kollidieren angesichts der Notwendigkeit, drei widerstreitende traditionelle Paradigmen des Gesundheitswesens auszubalancieren: Zugang, Kosten und Qualität. Kapitel Vier stellt konkrete rechtliche Formulierungen sowie Beispiele einer Umsetzung einer Reihe ethischer Prinzipien vor und erweitert diese mit einem zusätzlichen ethnischen Prinzip, welches auf internationale klinische Studien Anwendung findet. Kapitel Fünf stellt eine

vergleichende Analyse des rechtlichen Rahmens für klinische Studien in der Europäischen Union und den Vereinigten Staaten von Amerika dar. Kapitel Sechs konzentriert auch auf das Thema der Registrierung klinischer Studien. Das Ziel einer verpflichtenden Registrierung wird in die Überlegungen dieser Dissertation eingebunden, da die globale Dimension von besonderer Bedeutung ist und die Entwicklung eines internationalen Standards diesbezüglich erfolgreich erreicht wurde dank der Interaktion verschiedener Akteure. Kapitel Sieben nimmt einen „praktischeren“ Ansatz ein. Es stellt die Ergebnisse einiger Interviews vor, die im Zusammenhang mit Sponsoren, Patienten- und Verbraucherorganisationen und Forschern entstanden sind, und stellt die Ergebnisse einer einfachen empirischen Analyse, gerichtet auf die Dynamik der Personeneinstellung, basierend auf einer Probe von 394 klinische Studien, vor.

Den Mehrwert, den die vorliegende Dissertation zu leisten vermag, kann in Form von vier Fragen dargestellt werden, wobei Elemente jedes Kapitels der Arbeit dazu beitragen, eine jeweilige Antwort zu formulieren.

(i) Die erste Frage bezieht sich auf die hinter der Regulierung klinischer Studien stehenden Begründung: Warum sollten klinische Studien Gegenstand legislativer Maßnahmen sein? Kapitel Zwei stellt einige Instrumente bereit, um eine positive Antwort auf diese Frage zu finden. Genauer gesagt ist die Regulierung klinischer Studien notwendig, um das Recht auf Gesundheit und das Recht auf Information vollständig zu respektieren und umzusetzen. Insbesondere bedeutet das Regulieren klinischer Studien, dass spezifische Fragen, in denen diese Rechte negativ beeinflusst werden, angesprochen werden. In diesem Zusammenhang bespricht Kapitel Zwei die Herausforderungen und Möglichkeiten, die mit den Fragen der Probandeneigenschaften, der konkreten Rekrutierung von Probanden, Placebo-gesteuerter klinischer Studien und Sorgfaltsstandards, der Registrierung klinischer Studien – welche auch in Kapitel Sechs diskutiert werden – und Einwilligungserklärungen zusammenhängen.

(ii) Die zweite Frage berücksichtigt die Schub- und Zugkräfte, die Legislativorganen im Bereich der Regulierung klinischer Studien begegnen: Welche Interessen müssen in der Regulierung klinischer Studien ausbalanciert werden? Um eine Antwort auf diese Frage zu geben, präsentiert Kapitel Drei eine Klassifizierung von Paradigmen klinischer Studien und widerstreitender Interessen. Es schlägt vor, dass Legislativorgane die

Interessen dreier Akteure berücksichtigen sollten – der teilnehmenden Probanden, Sponsoren und Forschern – und dass diese Interessen effektiv in Anbetracht dreier widerstreitender Paradigmen – Zugang, Kosten und Qualität – kategorisiert werden können. Die Kategorisierung von Themen klinischer Studien diesbezüglich repräsentiert einen eigenständigen Beitrag zur Literatur über klinische Studien. Darüber hinaus identifiziert Kapitel Vier mit Blick auf die Handlungen der Akteure eine Reihe von optimalen Vorgehensweisen (best practice), die private Akteure berücksichtigen könnten, um den Schutz des höchstmöglichen ethischen Standards in klinischen Studien sicherstellen zu können.

(iii) Die dritte Frage berücksichtigt die Thematik der Zuweisung von Kompetenzen in der Regulierung klinischer Studien: Auf welcher intentionellen Ebene sollten klinische Studien reguliert werden? (Krankheits-)Zustände, die eine Behandlung benötigen, für die klinische Studien derzeit am Laufen sind, machen heutzutage wohl nicht vor nationalen Grenzen Halt – konsequenterweise sind klinische Studien weit davon entfernt, einen allein nationalen (und nationalistischen) Ansatz anzunehmen. In diesem Zusammenhang bestätigt die empirische Analyse, die in Kapitel Sieben enthalten ist (genauer, Unterkapitel V), dass die globalisierte Dimension klinischer Studien derzeit vorherrschend ist. Kurz gesagt stellt sie fest, dass die überragende Mehrheit der 394 klinischen Studien, die in der Studie aufgeführt sind, in mehr als einem Staat gleichzeitig Probanden rekrutiert und dass die überragende Mehrheit der 41 aufgeführten Staaten ein Interesse daran hat, die internationale Dimension der klinischen Studien, die Probanden in ihrem Staatsgebiet rekrutieren, anzuerkennen. Ferner lassen die Schlüsse aus Kapitel Zwei darauf schließen, dass die Natur einiger Herausforderungen, die im Bereich klinischer Studien herausragend sind – insbesondere Themen wie die lokalen Standards der Pflege, Registrierung und Einwilligungserklärung in internationalen klinischen Studien – die Förderung legislativer Bemühungen auf internationaler Ebene erfordern, da sie Rechte berühren, die den (menschlichen) Probanden als solchen zustehen und nicht an nationale Grenzen gebunden sind (bzw. sein sollten). Bezüglich der Teilung der Kompetenzen zwischen der internationalen und nationalen Ebene schlägt Kapitel Vier vor, das Vertrauen und Verlassen auf das Prinzip der Subsidiarität stetig als Maßnahme, um Gesetzgebung zu klinischen Studien vollständig und effektiv auf der angemessenen Ebene institutioneller Macht umzusetzen, einzubringen.

(iv) Die vierte Frage berücksichtigt die Herausforderungen, denen Legislativmaßnahmen begegnen, insbesondere, wenn sie unter Berücksichtigung der Antwort auf die dritte Frage umgesetzt werden: Wie sollte die Legislative den globalisierten Bereich klinischer Studien regulieren? Die Ergebnisse dieser Dissertation in diesem Zusammenhang können in drei Indikatoren zusammengefasst werden. Erstens sollte die Legislative – sei es auf nationaler, regionaler oder internationaler Ebene – sich der Art der Herausforderungen klinischer Studien, der durch klinische Studien berührten Interessen und der erfolgreichen, bereits auf internationaler Ebene entwickelten Dynamik bewusst sein. In diesem Sinne bestätigen Kapitel Drei und Sieben (Unterkapitel II-IV, die sich mit der Beschreibung der Ansichten, die durch Bündel von Akteuren geäußert wurden, auseinandersetzen), dass die Interessen der Akteure auf jeder institutionellen Ebene Bedeutung haben. Ferner wird in Kapitel Sechs in die Entwicklung der ICTRP ein Beispiel einer erfolgreichen Interaktion der ergänzenden regulierenden Anstrengung gelesen, die durch öffentliche Autoren und die wissenschaftliche Gemeinschaft beworben wurde. Zweitens wird die globale Natur klinischer Studien insbesondere in den Fällen legislativer Anstrengungen bezüglich multiregionaler klinischer Studien und des Imports von im Ausland erhobener Daten relevant. Daher wird in Kapitel Fünf eine vergleichende Analyse der Regelungen dargestellt, die in der EU und den USA bezüglich globalisierter klinischer Studien eingeführt wurden. Die Analyse identifiziert Ähnlichkeiten und Unterschiede der zwei Systeme, um sowohl privaten Akteuren mit Interessen im Bereich Compliance als auch institutionellen Akteuren mit Interessen in der Reformierung des Rechts eine aktuelle vergleichende Analyse zur Verfügung zu stellen. Angesichts dessen, dass letztere auf der neuen europäischen Verordnung über klinische Prüfungen basiert – welche in Kürze in Kraft treten wird und bislang noch nicht Gegenstand ausführlicher Literaturbeiträge war –, repräsentiert insbesondere sie eine eigenständige Analyse im Bereich der Literatur bezüglich klinischer Prüfungen. Sie wird darüber hinaus ergänzt durch ein Addendum des Status der europäischen Verordnung über klinische Prüfungen in vier Mitgliedstaaten, die sich während der Erstellung der vorliegenden Dissertation darauf verständigt haben, Informationen zu teilen. Drittens können globalisierte klinische Studien nicht reguliert werden, ohne dass die Notwendigkeit der effektiven Umsetzung gemeinsamer ethnischer Standards hohe Berücksichtigung findet. Daher beinhaltet Kapitel Vier der vorliegenden Dissertation konkrete Hypothesen bezüglich der Ausgestaltung, die solche Standards innerhalb der Gesetzgebung im Bereich klinischer Studien erfahren soll, unter Berücksichtigung der

Herausforderungen, die durch das Phänomen des „Outsourcing“ klinischer Studien in Entwicklungsländer hervorgerufen werden.

Abschließend ist festzustellen, dass die vorliegende Dissertation durch die oben beschriebenen Kapitel darauf abzielt, einen eigenständigen Beitrag im Bereich des Rechts klinischer Studien und dessen Praxis im internationalen Szenario abzubilden. In diesem Zusammenhang stellen wohlüberlegte legislative Anstrengungen, die die komplexen Dynamiken – hinsichtlich der involvierten Interessen, ethnischen Überlegungen und geographischen Herausforderungen – berücksichtigen, das beste Werkzeug dar, um Licht auf die Risiken und Chancen des Probandenschutzes in klinischen Studien zu werfen.

(2) Erklärung

Hiermit erkläre ich ehrenwörtlich,

- daß mir die geltende Promotionsordnung der Fakultät bekannt ist;
- daß ich die Dissertation selbst angefertigt habe und alle von mir benutzten Hilfsmittel, persönlichen Mitteilungen und Quellen in meiner Arbeit angegeben habe;
- daß die Hilfe eines Promotionsberaters nicht in Anspruch genommen wurde (falls doch zutreffend, Umfang der Unterstützung angeben);
- daß Dritte weder unmittelbar noch mittelbar geldwerte Leistungen von mir für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt meiner vorgelegten Dissertation stehen;
- daß ich die Dissertation noch nicht als Prüfungsarbeit für eine staatliche oder andere wissenschaftliche Prüfung eingereicht habe;
- daß ich weder die gleiche, eine in wesentlichen Teilen ähnliche oder eine andere Abhandlung bei einer anderen Hochschule als Dissertation eingereicht habe (falls doch zutreffend, dies bitte angeben und ggf. mit welchem Ergebnis).

Desweiteren erkläre ich mich damit einverstanden, dass die elektronische Version der Dissertation einer Überprüfung der Einhaltung der Grundsätze zur Sicherung guter wissenschaftlicher Praxis unterzogen wird.

Jena, 31.12.2017



Claudia Muttin

*(3) Lebenslauf [Redacted in the Electronic Copy]*



# Clinical Trials Law and Policy: Human Subjects Protection and Global Dynamics in Clinical Trials

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CLAUDIA MUTTIN

JENA – DECEMBER 10, 2018



Friedrich-Schiller-Universität Jena

## Agenda

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- Introduction
  - Highlights
  - Research questions
  - Background
  - Hot topics
- Zoom in: two original contributions
  - Competing paradigms in clinical trials (CTs)
  - Surveys and empirical analysis
- Conclusions
  - Outcome
  - Next steps

# Introduction

## Highlights

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- Focus on risks and opportunities of a **globalized clinical research environment**, with the aim of providing some insights on how to improve human subjects' protection in clinical trials
- Focus on the global dimension of clinical trials and on their status and challenges in **developing economies vis-à-vis developed economies** and on the role that **different stakeholders** play in the field of clinical trials in the light of the need to balance their competing interests
- A variety of **approaches**: descriptive, comparative, and empirical

## Issue one: Why

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### Why should CTs be regulated?

See Chapter Two discusses the right to health and the right to information and **grey areas** such as:

- Sample tailoring
- Subjects' recruitment
- Placebo-controlled clinical trials and standards of care
- CTs registration
- Informed consent

## Issue two: How

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### How are CTs regulated?

- See Chapter Four identifies a series of **potential best practices** that private stakeholders may take into consideration to preserve the protection of the highest attainable ethical standards when conducting clinical research
- See Chapter Five presents a comparative analysis of the provisions implemented in the **EU** and the **US** with regard to globalizes CTs (including an addendum on the **CTR** application-framework)
- See Chapter Six reads in the development of the **ICTRP** as example of successful interaction of the complementary regulatory efforts promoted by public actors and the scientific community

## Issues 3 and 4: Who and Where

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### Which are the interests to be balanced in CTs regulation?

- Chapter Three presents a **model** (a “taxonomy”) that categorizes interests of CTs stakeholders in light of competing paradigms
- Chapter Seven presents the results of **surveys** conducted with sponsors, investigators, and patients

### At which institutional level should CTs be regulated?

- Chapter Seven presents the results of an **empirical analysis** regarding CTs in 41 countries

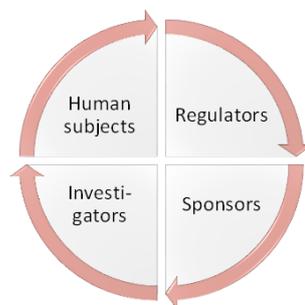
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## By way of background

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Clinical trial (**CT**): *“Any research study that prospectively assigns human participants or groups of humans to one or more health related interventions to evaluate the effects on health outcomes.”*

-- WHO, World Health Organization (2018)



- **Key stakeholders** in CTs (at any given level)
- **Four phases**

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## Grey areas

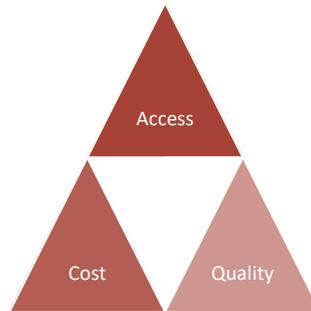
When is **consent** informed? Should placebo-controlled trials be conducted only when no best **proven** alternatives exist or when no **local** alternatives exist?



## Original Contributions

## (1) Gostin's model: revisited

Three **competing paradigms**: regulatory interventions affecting any of those paradigms will likely produce results on one or more of the others



And three **categories of stakeholders**: patients, sponsors, investigators

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## The taxonomy

	Access	Cost	Quality
Human Subjects	(1) Access to CTs (2) Public access to CT data	(1) Cost of participation (2) Cost of compliance	(1) Safety of CTs (2) Safety and effectiveness of the CTs' outcome
Investigators	(1) To sponsors (2) To CT data	(1) Costs of compliance	(1) Of CT data (2) Safety and effectiveness of the CTs' outcome
Sponsors	(1) To investigators (2) Disclosure concerns	(1) Costs of CTs <i>per se</i> (2) Costs of compliance	(1) Of CT data (2) Safety and effectiveness of the CTs' outcome

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# Relevance

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## How can the model help?

- Analysing the way in which each stakeholder – human subjects, investigators, and sponsors – develops specific concerns and interests within each paradigm provides us with a **better understanding** of the dynamics of CTs, both at local and at global levels
- Understanding the taxonomy helps to explain why the **global dimension of CTs** is now the dominant one (*escalation effect*)
- Contributing to **better predict** the results of clinical trials regulations and reforms

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## (2) “On the ground” analysis

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- **Surveys** conducted with CTs **sponsors, patients’ and consumer organizations, and investigators**. The interviews contribute to clarifying the approach and position of the main clinical trials’ stakeholders with regard to the current dimension and regulatory challenges of CTs
- Simple empirical analysis conducted on the basis of a sample of **394 ICTRP CTs**
- **Limits:** sample size



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## Survey I: sponsors (I)

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### Sample selection

- **Cross-industry** factor: biotechnology – therapeutics and diagnostics, biotechnology – research and development services, pharmaceutical, medical technology, and public and non-profit organizations
- **Geographical** factor: Africa, Asia, Europe, Central America, Oceania, South America, US and Canada
- **Four** sponsors agreed to participate in the research are based in the UK, Taiwan, Belgium, and in the US (on average, more than 15 CTs / year)

## Survey I: sponsors (II)

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- **10 questions**, including:
  - Countries in which the company/institution operates in the CTs field
  - Recruitment practices used by the company “abroad” (reliance on CROs)
  - Involvement of the company/institution in the transfer of foreign data
- All four sponsors interviewed – while engaged in different kinds of activities and based in different areas of the world – are active at the **international level**, confirming that even for such a small sample CTs have an international dimension
- Is an **international regulatory action** needed? The sponsors replied with opinions varying from point three and point seven in the Lickert scale

## Survey II: investigators (I)

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### Sample selection

- **15 investigators** agreed to participate in the survey
  - 10 investigators based in developed economies and five based in developing economies or economies in transition)
  - 10 investigators employed by Universities, two by a publicly funded governmental agency which engages in clinical research, two for a private company, and one for a mixed private-public research centre
- **10 questions**, including:
  - Location of the investigator's work, of her sponsor, and of the human subjects taking part in her clinical trial.
  - Possible reasons for which the investigator was selected by a specific sponsor.

## Survey II: investigators (II)

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- **No** prevalent international dimension of CTs in the operation of the investigators
- **Compliance** is driven by underlying interest in publishing their study, rather than the need to comply with legal provisions
- **No** absolutely positive opinion on the benefits associated with implementing an international binding CTs regulation

# ICTRP: empirical analysis

**Underlying question:** at which institutional level should CTs be regulated?

**Sub-goals:**

- Test to which extent CTs have **“gone global”**
- Assess whether **some countries** are more affected by such globalization than others
- Estimate whether there is a **correlation** between the extent to which CTs conducted in countries are “international” in size, and their economic status (*i.e.*, developed economies, developing economies or economies in transition).



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# Sample selection

- **53 countries** randomly selected from the “Country Classification” section included in the United Nations World Economic Situation and Prospects for year 2017
- For each of the countries a search on the WHO ICTRP was conducted.
- **Search variables:**
  - Phase I to VI of clinical trials
  - Country
  - Date of registration

**Data utilized:** top 10 results (plus adjustments e.g., halted recruitment or have less than 10 recruiting trials) *i.e.*, **394 CTs in 41 countries**

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## Relevant countries



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## Data pooling

Table 8  
Clinical Trials sampled to assess their degree of "globalization"

Country	Developed or Developing/in Transition	N° Clinical Trials Sampled	N° Recruitment Countries (average)
Iceland	Developed	10	39,5
Bahrain	Developing/Tr.	7	35,1
Algeria	Developing/Tr.	10	34,9
Bulgaria	Developed	10	33,1
Bosnia and Herzegovina	Developing/Tr.	10	32,0
Bolivia	Developing/Tr.	7	31,1
Morocco	Developing/Tr.	10	29,2
Cameroon	Developing/Tr.	9	27,4
New Zealand	Developed	10	27,3
Uruguay	Developing/Tr.	7	25,7
Denmark	Developed	10	21,5
United Kingdom	Developed	10	21,1
Guatemala	Developing/Tr.	10	19,2
Romania	Developed	10	19,2
Croatia	Developed	10	17,5

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## Results

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- **Only four** countries host on their territory clinical trials that recruit only within national borders (*hypothesis confirmed*)
- **Some countries** host clinical trials that recruit in a pool of other countries relatively smaller than others (*hypothesis confirmed*)
  - For example, CTs that take place in Switzerland on average recruit in Switzerland and in one other country; CTs that take place in Algeria on average recruit in Algeria and in 33 other countries
- The existence of a strong **correlation** between the extent to which clinical trials conducted in countries are “international” in size and their economic status is **not supported** by the findings of this research (*hypothesis not confirmed*)

## Conclusions

## Outcome (I)

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### **Why should CTs be regulated?**

- In order to fully respect and implement the right to health and the right to information
- In particular, regulating CTs means to address specific issues (*i.e.*, grey areas) in which those rights may be negatively affected

### **How are CTs regulated?**

Efforts to regulate CTs are far-reaching, as confirmed by the analysis of the EU and US legal frameworks. Currently, important regulatory challenges regard multi regional clinical trials and the import of foreign-obtained data

## Outcome (II)

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### **Which are the interests to be balanced in CTs regulation?**

- The interests of human subjects, sponsors, and investigators (*balancing exercise*)
- Vis-à-vis trade-offs between three competing paradigms: cost, access, and quality

### **At which institutional level should CTs be regulated?**

The globalized dimension of CTs is currently prevalent. The nature of some of the challenges that are prominent in the field of CTs require legislative efforts to be effective on the global level

## Next steps

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### Short-term expansions:

- Expansion of Chapter Five, including **secondary sources** and an overview of the **pre-CTR legal framework**
- Run an **updated version** of the empirical analysis

### Long-term expansions:

- Expansion of the comparative analysis, to include **other jurisdictions** and ICH standards
- Expansion or analysis of relevant legislation to include **pharmacovigilance** and **marketing authorization processes**

Questions?