Indian Journal of Law and Technology

Volume 16 | Issue 1 Article 5

2020

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I. Introduction

The purpose of this article is to illustrate the basic tenets of European Union law on clinical trials. Such body of law has been progressively harmonized in the European Union over the years with the aim of subjecting interventional clinical trials conducted in any of the 27 European Union Member States to identical rules.

The article initially describes the reasons why clinical trials are important to measure the safety, efficacy and cost-effectiveness of innovative medical treatment. It then continues by illustrating the scope and basic principles of the current EU Regulation, as well as its main changes over the previous legislation. Further, the article explains the requirements of the scientific and the ethical approvals of a clinical trial application. Lastly, the authors focus on the patients' consent to the enrolment in a clinical trial, as well as to the patients' separate consent to the processing of their personal data.

* The authors are Partners, Gitti and Partners, with an expertise in commercial and corporate law and regulatory matters. They would like to thank Karthik Rai and Vasu Agarwal, students at the National Law School of India University, for their invaluable research assistance in coming up with this paper.

The European Union harmonized body of law is not only relevant within the EU borders: European Union rules also play a significant role for contract research organizations and research institutions operating outside the European Union because – as the article points out - clinical trials conducted outside the European Union, but referred to in a clinical trial application within the European Union, must comply with regulatory requirements that are at least equivalent to those applicable in the European Union.

II. Drug Clinical Trials: Why, Who and What

2.1 Drug Clinical Trials: Why They Matter. Recently, the Covid-19 pandemic crisis has shown that innovation is key to resolving this momentous health issue: "*In these extraordinary circumstances, we need to unleash the full power of science, to deliver innovations that are scalable, usable, and benefit everyone, everywhere, at the same time*".[1] However, some[2] argue that "[…] *the continued expansion of health care costs is largely the result of innovation that tends to have low productivity*". As States, as well as private citizens, invest tremendous resources in healthcare,[3] it is important to identify medicinal products and med-tech solutions that are safe, efficacious and cost-effective.

Clinical trials are a key tool through which new drugs are ultimately measured. "*Clinical trials can show researchers what does and doesn't work in humans that cannot be learned in the laboratory or in animals*".[4] The healthcare industry, as well as physicians,[5] rely on research that tests medicinal products throughout various phases of scientific trials, as "*External clinical evidence both invalidates previously accepted diagnostic tests and treatments and replaces them with new ones that are more powerful, more*

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1 WHO Director-General's opening remarks at the media briefing on COVID-19 – 15 May 2020.

2 Eli M. Cahan, Robert Kocher Roger Bohn 'Why Isn't Innovation Helping Reduce Health Care Costs?' *Health Affairs Blog* of June 4, 2020.

3 Erixon, Fredrik, and Erik Van der Marel, 'What is Driving the Rise in Health Care Expenditures?: An Inquiry into the Nature and Causes of the Cost Disease.' *European Centre for International Political Economy*, 2011.

4 Robert L. Ferris, MD, PhD, in LifelineLetter, March/April 2017.

5 Evidence based medicine relies on the best available external clinical evidence. "*By best available external clinical evidence we mean clinically relevant research, often from the basic science of medicine, but especially from patient centred clinical research into the accuracy and precision of diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens*." *Sackett, David L., et al* 'Evidence Based Medicine: What it is and What it isn't: It's About Integrating Individual Clinical Expertise and the Best External Evidence,' *BMJ: British Medical Journal*, vol 312, Nos 7023, 1996, pp 71–72.

accurate, more efficacious, and safer."[6] In conclusion, "*Randomized controlled trials are the gold standard tool for evaluating interventions*".[7]

2.2 The Actors on the Stage of Clinical Trials. Clinical trials always require at least three different subjects working together:

(a) a sponsor of the trial, i.e., an individual, company, institution or organization which takes responsibility for the initiation, management and financing of the clinical trial;

(b) an investigator, who is an individual responsible for the conduct of a clinical trial at a clinical trial site;

(c) a clinical trial site where the trial is conducted; and

(d) patients who participate in a clinical trial either as recipients of an investigational medicinal product or as part of a control group.

The "script" of the clinical trial is set out in the protocol of the clinical trial, which is defined as "*a document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial.*"[8]

It is of paramount importance that all the above subjects have specifically regulated roles and responsibilities, so they may work in-sync in order to obtain reliable data that can be the basis of clinical findings. As it has been stated,[9] "*It is only with open dialogue that sponsors, health care providers, government regulators and – most importantly – trial participants and the public will become comfortable that clinical trials are not exploitative but fair, necessary and often beneficial. Transparency in that debate and dialogue is critical.*"

III. Clinical Trials in the European Union

3.1 Clinical Studies vs. Clinical Trials. According to the current definition given by the European Union Regulation number 536/2014 (hereinafter the "***Regulation***"), a clinical study is a simpler investigation compared to a clinical trial. In fact, while a clinical study intends to discover the effects of a

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[6] Again, Sackett, David L., et al 'Evidence Based Medicine: What it is and What it isn't: It's About Integrating Individual Clinical Expertise and the Best External Evidence,' BMJ: British Medical Journal, vol 312, Nos 7023, 1996, pp 71–72.

[7] Ioannidis, John P.A. 'Clinical Trials: What a Waste,' BMJ: British Medical Journal, vols 349, 2014.

[8] The definition of "protocol" is provided by art 2.2(22) of the Regulation.

[9] Li, Rebecca, et al 'Global Clinical Trials: Ethics, Harmonization and Commitments to Transparency,' Harvard Public Health Review, vol 6, 2015, pp. 1–7.

medicinal product, identify adverse reactions and study its functioning in the human body,[10] a clinical study "upgrades" to a clinical trial, or interventional trial, when the investigation does not fall within normal clinical practice.[11]

In other words, a clinic trial entails, by its nature, a deviation from standard clinical practice and, as such, is subject to additional legal requirements, given that the clinical trial may pose new risks to the safety of the study subject arising "*from two sources: the investigational medicinal product and the intervention*".[12]

The Regulation applies only to drug clinical trials (and not to clinical studies in general, or non-interventional studies). In fact, the deviation from the normal clinical practice – which defines, instead, clinical trials - represents the key factor reflecting additional risks and justifying a more rigorous approach.The distinction between interventional and non-interventional studies is of the utmost importance, as the inclusion of a certain clinical study in one category or the other could lead to greater freedom for Member States, who are not bound by the provisions of the Regulation with regard to non-interventional studies.

Regulators will also need to be careful that studies, which are interventional in nature, are not mislabelled as non-interventional. In such case, a trial posing higher risks to patients would be concealed as posing no risks for patients and the stricter regime set out in the Regulation would be circumvented.

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[10] The following definition of clinical study is provided by Article 2.2(1) of the Regulation: "[...] *an investigation relating 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 (c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products.*"

[11] The following definition of clinical trial is provided by Article 2.2(2) of the Regulation: "[...] *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; the decision to prescribe the investigational medicine product is taken together with the decision to include the subject in the clinical study; or diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects".*

[12] Preamble No 11 of the Regulation.

IV. European Union Legislation on Clinical Trials on Drugs: Main Principles and how it Evolved

4.1 EU Directive 2001/20/CE. The European Union has recognized the importance of the issue of clinical trials and attempted to provide harmonized regulatory solutions for the past 20 years. The initial effort to harmonize regulations of various Members States occurred through a directive. According to European Union law, a directive is only binding as to its goals, while Member States are free to enact different provisions in order to reach such goals.

Directive number 2001/20/CE (hereinafter the "***Directive***") was enacted in 2001 in order to provide certain basic rules mandatory for Member States in relation to drug interventional trials (non-interventional or observational trials are not covered by the Directive and are mostly regulated by national legislation of Member States). The main goal of the Directive was to ensure the application of good clinical practice in the conduct of clinical trials.[13]

The Directive concerns clinical trials of medicinal products and does not apply to non-interventional clinical trials. The principal aim of the Directive is the protection of clinical trial subjects.[14] Further protection measures are constituted by the role of a qualified physician acting as investigator in the trial and the requirement that the trial must be conducted in compliance with good clinical practice.

Further, the Directive provides that a clinical trial, prior to it being conducted, has to be authorized by at least two distinct bodies: (1) a national competent authority, which assesses compliance with the Directive's requirements, and (2) an ethical committee, that each Member State is free to regulate.[15] The clinical trial is thus separately assessed both from a scientific and an ethical point of view.

The ethical point of view has always been an important pillar of European Union clinical trial regulations, and remains so on the basis of the idea that

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[13] In Italy such Directive has been implemented by means of Legislative Decree No 211/2003, while other European members had issued their own national laws.

[14] "*[…] a clinical trial may only be undertaken if the risks to the subject are not disproportionate to the potential benefits of the medical research. On the other hand, the right of the subject to physical and mental integrity must be respected, as well as the right to privacy.*" From the summary of the Directive provided on the EUR LEX website:<https://eur-lex.europa.eu/legal-content/EN/LSU/?uri=CELEX:32001L0020>.

[15] According to the definition of 'Ethics committee' provided by the Regulation, such committee should take into account the views of laypersons, in particular patients or patients' organisations.

human beings' needs and dignity should never be neglected. It is in fact possible to imagine a potential conflict between scientific research, aiming at discovery and innovation, and the safety, wellbeing and dignity of human beings. Clinical research should never go "too far" and thwart the rights of individuals, which must always be protected, and such protection cannot be limited to requesting consent of the study subject.

4.2 Goals of Simplification and Harmonization Fail under the Directive. It is widely accepted that the Directive did not achieve its intended goals of harmonization (i.e., making uniform the various national rules of single Member States)[16] and of simplification (allowing an expedite assessment of the trial application).[17] In fact, the Directive has been heavily criticized by researchers,[18] as well as by sponsors and patients' associations. As admitted also by the European Union legislator, "*[…] the Clinical Trials Directive is arguably the most heavily criticised piece of EU-legislation in the area of pharmaceuticals. This criticism is voiced by all stakeholders - patients, industry, and academic research*"[19] and "*[…] experience shows that a harmonised approach to the regulation of clinical trials has only been partly achieved. This makes it in particular difficult to perform a given clinical trial in several Member States.*"[20]

The system set up by the Directive in fact prolonged the average waiting time to commence clinical trials, increased the costs of conduct of the trial (both the trial costs and the insurance costs), and significantly decreased the number of trials conducted under the Directive. In 2009/2010 the European Commission arranged for a public consultation on the Directive, which

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[16] Hartmann, M. 'Impact Assessment of the European Clinical Trials Directive: A Longitudinal, Prospective, Observational Study Analyzing Patterns and Trends in Clinical Drug Trial Applications Submitted Since 2001 to Regulatory Agencies in Six EU Countries', Trials 13, 53 (2012).

[17] Giannuzzi V., Altavilla A., Ruggieri L., Ceci A. 'Clinical trial application in Europe: what will change with the new regulation?' Sci Eng Ethics. 2016; 22: 451-466.

[18] "*According to the Council of the European Union, between 2007 and 2011 the number of applications for clinical trials decreased by 25% in the EU. This is partially attributed to the Clinical Trials Directive of 2001, which ensured a high level of patient safety, but an unfavorable regulatory framework not only for pharmaceutical companies, but also for academic research in general. The Directive caused, for example, increases in staff requirements for sponsors, insurance fees, and administrative costs. As a result, many pharmaceutical companies and academic researchers felt discouraged to submit new applications within the EU.*" Yves Geysels, Christopher A. Bamford, Richard H. Corr 'The New European Union Regulation for Clinical Trials', Clinical Researcher, The Association of Clinical Research Professionals, February 1, 2017.

[19] Paragraph 1 of the Proposal of the Regulation proposal: <https://ec.europa.eu/health//sites/health/files/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf>.

[20] Preamble 4 of the Regulation.

exposed its weaknesses.[21] In short, the European Union had become a much less attractive region for conducting multi-centre clinical trials.

The Goals of the 2014 Regulation. The Regulation was born to address the Directive's shortcomings, and particularly to target the goals of harmonization and simplification in this field, also with a view of making Europe a competitive region in the global clinical trials market.

4.3.1 Harmonization. With regard to harmonization, the Regulation is a different legislative instrument compared to a directive: while a directive is only binding on Member States with regard to its goals, a regulation applies in the exact identical way in all Member States. Given that the letter of clinical trial rules will be identical rules in all 27 Member States, it would appear that the goal of harmonization is within easy reach. However, in practice, certain areas of the Regulation are still left to Member States' legislation. In particular, as it will be better illustrated in paragraph 5 below, the ethical revision of trials continues to be up to ethical committees, which Member States may regulate autonomously ("*The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned*"[22]).

4.3.2 Simplification. A second important achievement of the Regulation is the unification of the process of authorization of the trial, which will be coordinated among national competent authorities. The earlier de-centralized system will be replaced by a centralized system, whereby a single application dossier will be submitted to all the Member States concerned through a single submission portal (hereinafter the "***EU Portal***"). The process of authorization entails the cooperation of various national competent authorities involved in the authorization of the trial, which will however lead to a single decision. The same EU Portal will be used to notify the sponsor of such decision, setting forth "*as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether authorisation is refused*".[23] Such EU Portal will also be used as a single database for any safety communication relating to the safety of the study drug and of the trial. It is expected that the cooperation of Member States through this digital platform will also lead to easier authorization and conduct of multi-centred European Union clinical trials.

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[21] The responses of the consultation can be found here: <https://ec.europa.eu/health/sites/health/files/files/clinicaltrials/2010_03_30_summary_responses.pdf>.

[22] Art 4 para 2 of the Regulation.

[23] Art 8 of the Regulation.

4.4 Open Results of the Trial. Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor must submit to the European Union database a summary of the results of the clinical trial, accompanied by a summary written in a manner that is understandable to laypersons.[24] The ability to have open and shared sets of clinical data will enable researches to have access to grounds for further research.[25]

4.5 Novelties and Other Aspects of the Regulation. It is clear that most innovations will be a consequence of the implementation of the EU Portal. This feature of the Regulation is quite meaningful as it has been noted that "*Perhaps the most significant novel aspect of the Clinical Trial Regulation is the establishment of the EU Portal, a "one-stop shop" through which sponsors can apply for an authorization to conduct a clinical trial in any number of Member States.*"[26]

Great benefits in terms of harmonisation will also derive from the uniform set of documents, listed in Annex I of the Regulation, which will be required for the application. Such documents will be the same across the European Union and will include a cover letter, the complete European Union application form, the protocol, the investigator's brochure, the documentation relating to the compliance to good clinical practices and the investigational medicinal product dossier. Such uniform set of documents, once the EU Portal will be available, will surely simplify the submission of the applications, regardless of the Member States involved in the process.

The Regulation also introduced the Clinical Trials Coordination and Advisory Group ("**CTAG**")[27]. The new body will serve as a forum for exchanging best practices between Member States, in accordance with the harmonisation goal pursued by the Regulation. In particular, CTAG will: (i) support the exchange of information between the Member States and the Commission on the experience acquired with regard to the implementation

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[24] Art 37 para 4 of the Regulation.

[25] "*With each of these advances we get closer to having all trials registered and all results reported. The next challenges are how to normalise and standardise the release of anonimysed individual patient data from trials and how to restore hidden data from old trials. But let's pause briefly to appreciate how far we have already come.* Europe's drug regulators and legislators, and everyone who has campaigned for and supported transparency, deserve much credit for holding their nerve and doing the right thing for public health." Groves, Trish. 'Big Strides in Europe towards Clinical Trial Transparency' BMJ: British Medical Journal, vol 349, 2014.

[26] Pavlou, Anna, and Emmanuel Saurat. 'Clinical Trials Regulation: A Further Step towards Increased Medical Innovation in the EU,' European Journal of Risk Regulation, vol 6, No 4, 2015, pp 646–648.

[27] Art 85 of the Regulation.

of the Regulation; (ii) assist the Commission in providing the support for the cooperation of Member States; and (iii) draft recommendations on criteria regarding the selection of a reporting Member State.

4.6 The Entry into Force of the Regulation. The EU Portal, as well as the European Union database where all information submitted through the EU Portal will be stored, supposedly one of the highpoints of the Regulation, is probably its worst enemy so far. In fact, the entry into force of the Regulation shall occur six months after the publication of a notice whereby the European Commission confirms that the EU Portal and the EU database have achieved full functionality and the systems meet the required functional specifications. This has not happened yet, although the Commission has continued to state that this is imminent.[28] Therefore, so far, the Directive continues to apply, while some argue that the Regulation – that appeared cutting edge in 2014 – already shows the signs of age.

V. Ethical Review of Clinical Trials

5.1 The *Rationale* behind the Ethical Review. The previous section of this article focused on the required authorization by regulatory authorities of a clinical trial from a scientific standpoint. We now turn to consider the other fundamental requirement for clinical trials: ethical approval of trials. In fact, the Regulation provides for an additional and separate assessment of a proposed clinical trial: an ethical review of the trial at a national level. This further assessment allows the process to develop also outside the scientific arena and to involve patients and citizens, who obviously need to trust the sponsors and investigators, but have the statutory right to be directly involved.

Although the Regulation does not expressly state the *rationale* behind the need for an ethical review, the importance of such ethical assessment can be inferred by certain indications given by the Regulation in its introductory preambles. For example, Preamble 18 of the Regulation sets forth that ethical reviews are required in order to ensure the involvement of laypersons, in particular patients or patients' organisations, in the process.

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[28] "*Due to technical difficulties with the development of the IT systems, the portal's go-live date had to be postponed and therefore the EU Clinical Trial Regulation will come into application during 2020 instead of October 2018, as previously scheduled.*" (European Union Commission website). "*The product owners will work with EMA and the IT supplier to analyze and design these items in the first few months of 2020, in a way that ensures efficient delivery.*" (EMA website).

Further, the same Preamble also provides that ethics committees are meant to involve all the expertise necessary to look at the study from various points of view. In accordance with international guidelines, the ethical assessment should be carried out jointly by a reasonable number of persons who collectively have all the necessary qualifications and experience, without limitation to a single field. Such requirement can be set forth in different ways by Member States, but international guidelines, such as the World Health Organization's Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants, suggest including at least individuals with expertise in behavioral or social sciences, health care providers, experts in legal matters and/or ethics, and lay people, whose primary role is to share their insights about the communities from which participants are likely to be drawn.[29]

Ethics committees must be independent from the sponsor, the clinical trial site and the investigators involved, as well as free from any other undue influence. Such a principle is also mentioned in Preamble 18, but Member States are free to determine their implementing measures to guarantee independence. Again, international standards provide some guidance.[30] To ensure that the ethics committees cannot be pressured to approve or reject particular protocols, the ethics committee's membership should include at least one person with no connection to the organization that sponsors or conducts the trial. Moreover, researchers, sponsors and funders may attend the ethics committees' meetings only to answer questions about their research protocols and associated documents, but their participation shall not be allowed when the committee reaches decisions about the proposed research. Measures should also be taken to ensure that committees' members are protected from retaliation based on positions taken with respect to the review of research projects.

5.2 Discretion of Member States in the Field of Ethical Review. While the scientific assessment of clinical trials is subject to a detailed harmonised procedure by the Regulation,[31] the Regulation approach is completely different in relation to the ethical review of clinical trials. In fact, the Regulation

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[29] Standard 2 (Composition of research ethics committees) of WHO's Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants, <*https://apps.who.int/iris/bitstream/handle/10665/44783/9789241502948_eng.pdf;jsessionid=15A876B1B012E6A09A206E10E26F7155?sequence=1*>.

[30] Standard 4 (Independence of research ethics committees) of WHO's Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants, <*https://apps.who.int/iris/bitstream/handle/10665/44783/9789241502948_eng.pdf;jsessionid=15A876B1B012E6A09A206E10E26F7155?sequence=1*>.

[31] Arts 6 and 7 of the Regulation.

merely requires that the ethical review is performed by an ethics committee in accordance with the law of the Member State concerned.[32]

While such ethical review may encompass aspects listed in the Regulation, each Member State is granted with a fairly high degree of discretion to such regard: in fact, the mandatory provisions of the Regulation only require Member States to ensure that the timelines and procedures for the review by the ethics committees are compatible with the timelines and procedures set out in the Regulation for the scientific assessment of the application. In other words, the Regulation appears to be more concerned about the timing of the ethical review than the substance of it.

Such difference may allow Member States within the European Union to opt for different solutions with regard to the regulation of ethical reviews of clinical trials, thus impairing the goal of harmonization. Some States may even be ready to exploit this level of discretion and design their regulatory environment to be more attractive for the industry. Others may adopt or maintain a more restrictive ethical review framework. The Regulation thus allows for different ethical standards to coexist, if not to compete against each other.

Some have argued that the ethical committee's review under the Regulation is limited to the grounds set out in Articles 6 and 7 of the Regulation and thus is too restricted. "*In essence, this unreasonably limits the ethics committee to consideration of consent issues, confidentiality issues and suitability and recruitment of participants. This amounts to a drastic curtailment of the issues that ethics committees normally, and indeed must, consider.*"[33]

The timing of the ethical and the scientific reviews must be linked: Member States must complete the ethical review within completion of the scientific review process. With specific regard to timing of the scientific assessment, the Regulation grants to the reporting Member State a 10-day term from the submission of the dossier through the EU Portal to validate the application, taking into account the considerations expressed by the other Member States concerned, if any. Member States concerned can communicate any considerations relevant to the validation of the application within seven days from the submission of the application dossier.[34] From the validation of the dossier, the reporting Member State and each Member State concerned shall

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[32] Art 4 of the Regulation.

[33] Shaw, David, and David Townend "*Division and Discord in the Clinical Trials Regulation.*" *Journal of Medical Ethics*, vol 42, No 11, 2016, pp 729–732.

[34] Art 5 of the Regulation.

complete their assessment within 45 days.[35] Certain Member States have attempted to rationalize the previously existing network of ethical committees in order to render the ethical review of clinical trials more efficient and faster.[36]

VI. A Patient Perspective: Consent to Participation in The Study and Processing of Personal Data

6.1 Consent by the Study Subjects to Participate in the Clinical Trial. Our analysis of the Regulation would not be complete without focussing on a key requirement of a clinical trial: patients' consent. From the perspective of a patient, it is important to underline that no clinical trial can occur without the study subject expressly consenting to participate in it. In fact, long-standing ethical standards in the clinical research field require two basic components: informed consent and independent ethical oversight.[37] These components ensure that the participation of any individual in a clinical research is not only informed and free, but also complies with high ethical standards and respects human dignity.

The subject's consent under the Regulation aims at ensuring that ethical standards are met and the freedom of the patient is safeguarded.[38] Such consent is an essential requirement for the participation of the subject in a clinical trial. The Regulation sets forth such requirement in Article 29, which describes in detail all the information that must be provided to the patient in a prior interview with a member of the investigating team, in order to allow the patient to take an informed decision concerning the participation in the trial.[39] The information to be given to the patient includes, by way of

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[35] Art 7 of the Regulation.

[36] Italy, for example, had an impressive number of ethical committees, almost one for each hospital. Italian law n 3 of 2018 on clinical trials provides for a reduction and simplification of ethics committees, but delegates to further governmental decrees, not yet enacted, the promising results anticipated by the law. Therefore, Italy, which currently has a 20% share of the European Union's clinical trials, is attempting to set up a regulatory framework that will continue to render it an attractive destination for clinical trials, as evidenced by the eighteenth national report of the Italian Medicines Agency "AIFA" for year 2019, available here <*https://www.aifa.gov.it/documents/20142/241052/18-Rapporto-OsSC_03.10.2019.pdf/4694ddbe-8f65-68b4-ac3a-cd0e883fd982*>.

[37] European Data Protection Supervisor, "*A Preliminary Opinion on Data Protection and Scientific Research*", January 6, 2020.

[38] European Commission, "Questions and Answers on the interplay between the Clinical Trial Regulation and the General Data Protection Regulation".

[39] Art 29, para 2, of the Regulation provides that: "*Information given to the subject or, where the subject is not able to give informed consent, his or her legally designated representative for the purposes of obtaining his or her informed consent shall: (a) enable the subject or his or her legally designated representative to understand: (i) the nature, objectives,*

example, risks and inconveniences of the clinical trial and the patient's rights and guarantees (including the right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification). Furthermore, the information given to the patient must be comprehensive, concise, clear, relevant and understandable to a layperson.[40]

Once the patient is provided with all required information under the Regulation, the informed consent must be formalized in writing, must be dated and signed by both the patient and the member of the investigating team performing the interview with the patient. The Regulation also sets forth specific provisions applicable to particular categories of study subjects, in order to safeguard their rights and integrity, such as minors, incapacitated persons, pregnant or breastfeeding women.[41]

6.2 Consent to Allow Processing of Data within a Clinical Trial. The study subject must also expressly and separately allow for the processing of her/his personal data within the context of a clinical trial. Such consent cannot be implied by the consent to participate in the clinical trial.

The informed consent under the Regulation and the consent to the processing of personal data under the General Data Protection Regulation (EU)

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benefits, implications, risks and inconveniences of the clinical trial; (ii) the subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification; (iii) the conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial; and (iv) the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical trial is discontinued; (b) be kept comprehensive, concise, clear, relevant, and understandable to a layperson; (c) be provided in a prior interview with a member of the investigating team who is appropriately qualified according to the law of the Member State concerned; (d) include information about the applicable damage compensation system referred to in Article 76(1); and (e) include the EU trial number and information about the availability of the clinical trial results in accordance with paragraph 6."

[40] The risks of information overload have been often underlined: "*Adequately informing patients, as explained above, is key, but is a delicate and sensitive process that needs to be adapted to each patient's health literacy. The regulator, on the other hand, sees the need to inform patients from a more legalistic perspective. Different regulations accumulate what patients need to be informed about; consent via separate documents may sometimes be asked for (e.g. separate data protection or genetic testing documents), bringing the amount of information patients have to digest up to several dozens of pages. This approach does not help them to make an informed decision, as it may dilute the key questions patients need to focus on by the amount of administrative and legalistic details mandatory by law.*" Negrouk, Anastassia, et al "Clinical Trials, Data Protection and Patient Empowerment in the Era of the New EU Regulations" *Public Health Genomics*, vol 18, No 6, 2015, pp 386–395.

[41] Arts 31 to 35 of the Regulation.

2016/679 ("***GDPR***") are two distinct consents and serve different purposes. The consent under the Regulation aims at ensuring that ethical standards are met and the freedom of the patient is safeguarded.[42] Such consent is a procedural condition for the participation of the subject in a clinical trial. On the other hand, consent to the processing of personal data in the framework of a clinical trial allows the lawful processing of such data.

The entry into force of the GDPR brought novelties also with regard to the legal grounds for the processing of personal data in the conduct of clinical research. Consent to the processing of personal data in the framework of a clinical trial is one of the legal grounds allowing the lawful processing of personal data. Public interest and legitimate interest are also grounds for processing, which may be validly be used under certain circumstances.

With regard to the legal grounds of the processing, Member States appear to have taken different, often opposing, approaches. In certain instances, the consent of the patient to the processing of his/her personal data is viewed as essential for the conduct of the research. In other cases, the legitimate interest of the sponsor is considered to be the main ground for processing. While the debate is still open, the current interpretations and positions adopted by different Member States may end up undercutting one of the main goals of the GDPR, which was to ensure a uniform legal framework throughout the 27 Member States.

It should also be pointed out that, whenever consent is chosen as the legal ground for the processing of personal data in the framework a clinical study, such consent may always be withdrawn by the study subject pursuant to the provisions of the GDPR. If the subject withdraws his/her consent under the Regulation, such withdrawal does not necessarily affect the processing of data gathered in the trial. In fact, if the patient withdraws his/her consent under the GDPR, all data processing operations that were based on such consent remain lawful, but no further processing may occur and – if there is no other legal ground under the GDPR, such as legal obligations of the sponsor for purposes of ensuring safety – the data should be deleted.[43]

6.3 Interactions between the Regulation and Data Protection Legislation. The Regulation, which was devised in 2014 in order to overhaul the governance of clinical trials in the European Union, will become applicable in a legislative framework deeply changed by the subsequent entry into force

[42] European Commission, 'Questions and Answers on the Interplay between the Clinical Trial Regulation and the General Data Protection Regulation', April 10, 2019.

[43] European Commission, *Questions and Answers on the Interplay between the Clinical Trial Regulation and the General Data Protection Regulation*.

of the GDPR. The interconnection between the Regulation and the GDPR has been the subject of several studies by scholars and regulators. It has been recognized that the GDPR assigns to scientific research a more favourable regime,[44] but as of today there have been few comprehensive studies on the application of data protection rules to research.[45] As a consequence, several matters, questions and issues concerning the protection of personal data in the framework of clinical studies remain open for debate and interpretation, both at the European level and at Member States' level.

The outbreak of the COVID-19 pandemic prompted additional guidelines from European Union regulators and new guidelines were issued on April 21, 2020 by the European Data Protection Board.[46] Such guidelines clearly confirmed that consent is only one of the available legal bases for the processing of personal data under the GDPR and there is no ranking or preference among them. Furthermore, the guidelines reiterate that consent may not be a valid legal basis for data processing under certain circumstances, for instance if there is a clear imbalance between the study subject and the data controller (i.e., the research site or investigator). In this latter case, other legal bases, such as public interest, maybe more suitable to protect the rights of the patient to have his/her personal data processed according to the Regulation.

6.4 GDPR Only Partially Achieves Uniformity. One of the main goals pursued by the GDPR was to ensure a more uniform approach to data protection legislation across the European Union. In the past, the previous directive governing data protection in the European Union allowed Member States broad discretion in its implementation. This caused significant differences in legislation among the Member States and *de facto* hindered the conduct of

[44] The importance of scientific research for the ultimate benefit of individuals and society is enshrined in the GDPR itself (Recital 157 of the GDPR), which states that "*by coupling information from registries, researchers can obtain new knowledge of great value with regard to widespread medical conditions such as cardiovascular disease, cancer and depression. On the basis of registries, research results can be enhanced, as they draw on a larger population. Within social science, research on the basis of registries enables researchers to obtain essential knowledge about the long-term correlation of a number of social conditions such as unemployment and education with other life conditions. Research results obtained through registries provide solid, high-quality knowledge which can provide the basis for the formulation and implementation of knowledge-based policy, improve the quality of life for a number of people and improve the efficiency of social services. In order to facilitate scientific research, personal data can be processed for scientific research purposes, subject to appropriate conditions and safeguards set out in Union or Member State law*".

[45] European Data Protection Supervisor, "A Preliminary Opinion on Data Protection and Scientific Research", January 6, 2020.

[46] European Data Protection Board, *Guidelines 03/2020 on the Processing of Data Concerning Health for the Purpose of Scientific Research in the Context of the COVID-19 Outbreak*, April 21, 2020.

multinational/multi-centric clinical trials and studies in the European Union. The GDPR, being a regulation and not a directive, partially addressed such need for a more uniform legal framework.

However, the GDPR itself allows derogations by Member States on several matters, and national data protection authorities are still mainly responsible in their respective jurisdictions for the enforcement of the GDRP. Furthermore, on certain matters Member States appear headed towards different interpretations of the GDPR: for instance, certain Member States favour consent as the legal basis of choice for the processing of personal data within a clinical trial, whereas others are more inclined to favour public interest or legitimate interest as appropriate legal bases. Therefore, even if the GDPR enhanced uniformity throughout the EU, local data protection assessments of multinational research projects cannot be avoided entirely.

VII. Application of the Regulation Beyond EU Borders

7.1 Clinical Trials Conducted Outside the EU, but Referred to in an Application within the EU. The EU Regulation may also affect clinical trials conducted outside the European Union. In fact, according to Article 25 paragraph 5[47] of the Regulation, clinical trials conducted outside the European Union, but referred to in a clinical trial application within the European Union, must comply with regulatory requirements that are at least equivalent to those applicable in the European Union as regards the rights and safety of the subjects and reliability and robustness of the data generated in the clinical trial. Therefore, even when trials are conducted outside of the EU (for example, in India), it is essential to ensure that the principles of the Regulation are duly taken into consideration, if the data generated in such trials will be referred to in an EU application dossier.

Furthermore, European Union controls in Member States and third countries are mandatory under Article 79 of the Regulation. They will be carried out by the European Commission to ensure that clinical trials rules are being properly applied, even when trials are conducted outside the European Union.

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[47] "*Where the clinical trial referred to in paragraph 4 has been conducted outside the Union, it shall have been conducted in accordance with principles equivalent to those of this Regulation as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial*".

7.2 The 2015 Ban by the EU of Medicinal Products Tested in India and Developments in Indian Clinical Trial Legislation. The above discussed EU Regulation requirement echoes the 2015 suspension by the European Medicines Agency of about 700 medicinal products that were clinically tested by GVK Biosciences based in Hyderabad, India. The ban was recommended following an inspection at GVK Biosciences site at Hyderabad by the French medicines agency raising concerns over the conduct of clinical trials. It appeared that the studies conducted by GVK were flawed by systematic data manipulations that occurred over at least 5 years. The clinical studies results were therefore unreliable and thus it was recommended that, where no supporting data from other studies were available, the medicinal products were suspended. The European Medicines Agency reiterated a basic requirement: "*studies underpinning marketing authorisations in the EU are carried out to the highest standards and that the companies involved comply fully with all aspects of Good Clinical Practice (GCP)*".[48]

The European decision sparked intense political reactions on the part of the Indian government. In response, free trade talks with the European Union were cancelled by the Indian government. The then trade secretary Ms. Rita Teaotia said it was an "*expression of concern*" on India's part of an "*extremely disproportionate reaction to the perceived infringement*".[49] The Indian government, through the Central Drugs Standard Control Organization ("***CDSCO***"), probed the GVK Biosciences issue and found no manipulation of data. A further panel of experts engaged by the Indian government in October 2014 also found no manipulation of data after its investigation. The Indian government handled the GVK issue as a political and commercial problem: the Commerce Ministry said in a press release that it was "*disappointed by and concerned*" at the ban on "*one of the flagship sectors of India*".[50] The CDSCO never acted against Hyderabad's GVK Biosciences and no judicial cases about the GVK scandal ensued.

Nonetheless, the Indian government later strengthened its drug regulatory system. In particular, with regard to clinical trials regulations, the New Drugs and Clinical Trials Rules were enacted in 2019 (hereinafter the "***Rules***"). The Rules include several basic principles that appear to be aligned

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[48] See the May 21, 2015 opinion by the European Medicines Agency on case EMEA/H/A-31/1408.

[49] Asit Ranjan Mishra, 'India hardens stance on special safeguard mechanism at WTO' (*livemint*, 11 December 2015) <https://www.livemint.com/Politics/kk9eHd7iEqIM1GjpJgw1FN/India-hardens-stand-on-special-safeguard-mechanism-at-WTO.html>.

[50] 'India-The European Union (EU) FTA: The Intellectual Property Conflict' (*Coventus Law*, 14 August 2015) <http://www.conventuslaw.com/report/india-the-european-union-eu-fta-the-intellectual/>.

with those of the European Union Regulation on drug clinical trials, e.g., (i) Consent: trial subjects will be enlisted for trials only with prior informed consent; (ii) Ethical review: an ethics committee will monitor the trials; and (iii) Compensation in case of adverse events: in case of adverse events, trial subjects will be entitled to compensation for damages suffered.[51] The aim of the new Rules is to ensure that clinical trials in India are subject to predictable, transparent and effective regulations for such trials, also to the end of ensuring easier access to new drugs by the Indian population. Under the Rules, clinical trials must be approved by the Drugs Controller General of India following a specific application. Approval or rejection times vary depending on where the drug is developed: for drugs developed outside India further information may be sought within 90 days, while in case of an application for conducting clinical trial of a new drug or investigational new drug as part of discovery, research and manufacture in India, the application is to be decided within 30 days. In case of no communication from DCGI, the application will be deemed to have been approved.

As some scholars[52] have concluded about the developments of clinical trials in India, "*many of the well-meaning requirements imposed on researchers and sponsors beginning in 2013 chilled the clinical trial environment, yet the requirements also brought appropriate attention to complex ethical issues*."

VIII. Conclusions

The above overview of the European Union regulatory framework for clinical trials on drugs illustrates the core principles of the harmonized regimen in the EU. Such regimen is important beyond EU borders due to Article 25 paragraph 5 of the Regulation, mandating that clinical trials conducted outside the European Union, but referred to in a clinical trial application within the European Union, must comply with regulatory requirements that are at least equivalent to those applicable in the European Union.

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[51] In relation to adverse events, Drugs Controller General of India ("DCGI") S. Eswara Reddy said: "*In case of injury to clinical trial subject, medical management will be provided as long as required as per the opinion of the investigator or till such time it is established that the injury is not related to the clinical trial. Also, compensation in cases of death and permanent disability or other injury to a trial subject will be decided by the DCGI*," Reddy said.

[52] Barnes, Mark, et al, 'The Evolving Regulatory Landscape for Clinical Trials in India' *Food and Drug Law Journal*, vol 73, No 4, 2018, pp. 601–623.

Since the clinical trials industry is globally interconnected (as evidenced by the numerous trials that European pharmaceutical companies are conducting in Asia, especially in India[53]), the principles of European Union law may be a relevant benchmark for other jurisdictions, too. Furthermore, it is possible that principles of clinical trial legislations of various countries around the world (and not just Member States of the European Union) will converge in the future.[54]

[53] With regard to the percentage of clinical trials worldwide conducted in India, see Sandhiya Selvarajan, Melvin George, Suresh S. Kumar, and Steven Aibor Dkhar, 'Clinical Trials in India: Where do we Stand Globally', Perspective in Clinical Research, 2013 July-September; 4(3): 160–164.

[54] Discussions by US, EU and Japan regulators on certain issues point towards a greater coordination in various fields, including clinical trials. See, for example, the November 6, 2019 tripartite meeting's press release: <https://www.ema.europa.eu/en/documents/agenda/meeting-summary-ema-food-drug-administration-fda-pharmaceuticals-medical-devices-agency-pmda_en.pdf>.