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)

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

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(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Articles 114 and 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee[(1)],

After consulting the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure[(2)],

Whereas:

(1) In a clinical trial the rights, safety, dignity and well-being of subjects should be protected and the data generated should be reliable and robust. The interests of the subjects should always take priority over all other interests.

(2) In order to allow for independent control as to whether these principles are adhered to, a clinical trial should be subject to prior authorisation.

(3) The existing definition of a clinical trial as contained in Directive 2001/20/EC of the European Parliament and of the Council[(3)] should be clarified. For that purpose, the concept of clinical trial should be more precisely defined by introducing the broader concept of ‘clinical study’ of which the clinical trial is a category. That category should be defined on the basis of specific criteria. This approach takes due account of international guidelines, and is in line with the Union law governing medicinal products, which builds on the dichotomy of ‘clinical trial’ and ‘non-interventional study’.

(4) Directive 2001/20/EC aims to simplify and harmonise the administrative provisions governing clinical trials in the Union. However, 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. Scientific development, however, suggests that future clinical trials will target more

specific patient populations, such as subgroups identified through genomic information. In order to include a sufficient number of patients for such clinical trials it may be necessary to involve many, or all, Member States. The new procedures for the authorisation of clinical trials should stimulate the inclusion of as many Member States as possible. Therefore, in order to simplify the procedures for the submission of an application dossier for the authorisation of a clinical trial, the multiple submission of largely identical information should be avoided and replaced by the submission of one application dossier to all the Member States concerned through a single submission portal. Given that clinical trials carried out in a single Member State are equally important to European clinical research, the application dossier for such clinical trials should also be submitted through that single portal.

(5) As regards Directive 2001/20/EC, experience also indicates that the legal form of a Regulation would present advantages for sponsors and investigators, for example in the context of clinical trials taking place in more than one Member State, since they will be able to rely on its provisions directly, but also in the context of safety reporting and labelling of investigational medicinal products. Divergences of approach among different Member States will be therefore kept to a minimum.

(6) The Member States concerned should cooperate in assessing a request for authorisation of a clinical trial. This cooperation should not include aspects of an intrinsically national nature, such as informed consent.

(7) In order to avoid administrative delays for starting a clinical trial, the procedure to be used should be flexible and efficient, without compromising patient safety or public health.

(8) The timelines for assessing an application dossier for clinical trials should be sufficient to assess the file while, at the same time, ensuring quick access to new, innovative treatments and ensuring that the Union remains an attractive place for conducting clinical trials. Against this background, Directive 2001/20/EC introduced the concept of tacit authorisation. This concept should be maintained in order to ensure that timelines are adhered to. In 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.

(9) Clinical trials for the development of orphan medicinal products as defined in Regulation (EC) No 141/2000 of the European Parliament and of the Council[(4)] and of medicinal products addressed to subjects affected by severe, debilitating and often life-threatening diseases affecting no more than one person in 50 000 in the Union (ultra-rare diseases) should be fostered.

(10) Member States should efficiently assess all clinical trials applications within the given timelines. A rapid yet in-depth assessment is of particular importance for clinical trials concerning medical conditions which are severely debilitating and/or life threatening and for which therapeutic options are limited or non-existent, as in the case of rare and ultra-rare diseases.

(11) The risk to subject safety in a clinical trial mainly stems from two sources: the investigational medicinal product and the intervention. Many clinical trials, however, pose only a minimal additional risk to subject safety compared to normal clinical practice. This is particularly the case where the investigational medicinal product is covered by a marketing authorisation, that is the quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure" or, if that product is not used in accordance with the terms of the marketing authorisation, that use is evidence- based and supported by published scientific evidence on the safety and efficacy of that product, and the intervention poses only very limited additional risk to the subject compared to normal clinical practice. Those low-intervention clinical trials are often of crucial importance for assessing standard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health. Those 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. The published scientific evidence supporting the safety and efficacy of an investigational medicinal product not used in accordance with the terms of the marketing authorisation could include high quality data published in scientific journal articles, as well as national, regional or institutional treatment protocols, health technology assessment reports or other appropriate evidence.

(12) The Recommendation of the Organisation for Economic Cooperation and Development (OECD) Council on the Governance of Clinical Trials of 10 December 2012 introduced different risk categories for clinical trials. Those categories are compatible with the categories of clinical trials defined in this Regulation as the OECD Categories A and B(1) correspond to the definition of a low-intervention clinical trial as set out in this Regulation, and the OECD Categories B(2) and C correspond to the definition of a clinical trial as set out in this Regulation.

(13) The assessment of the application for a clinical trial should address in particular the anticipated therapeutic and public health benefits (relevance) and the risk and inconvenience for the subject. In respect of the relevance, various aspects should be taken into account, including whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment of medicinal products and the authorisation of their placing on the market and whether surrogate end-points, when they are used, are justified.

(14) Unless otherwise justified in the protocol, the subjects participating in a clinical trial should represent the population groups, for example gender and age groups, that are likely to use the medicinal product investigated in the clinical trial.

(15) In order to improve treatments available for vulnerable groups such as frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders, medicinal products which are likely to be of significant clinical value should be fully and appropriately studied for their effects in these specific

groups, including as regards requirements related to their specific characteristics and the protection of the health and well-being of subjects belonging to these groups.

(16) The authorisation procedure should provide for the possibility to extend the timelines for the assessment in order to allow the sponsor to address questions or comments raised during the assessment of the application dossier. Moreover, it should be ensured that, within the extension period, there is always sufficient time for assessing the additional information submitted.

(17) The authorisation to conduct a clinical trial should address all aspects of subject protection and data reliability and robustness. That authorisation should therefore be contained in a single administrative decision by the Member State concerned.

(18) It should be left to the Member State concerned to determine the appropriate body or bodies to be involved in the assessment of the application to conduct a clinical trial and to organise the involvement of ethics committees within the timelines for the authorisation of that clinical trial as set out in this Regulation. Such decisions are a matter of internal organisation for each Member State. When determining the appropriate body or bodies, Member States should ensure the involvement of laypersons, in particular patients or patients' organisations. They should also ensure that the necessary expertise is available. In accordance with international guidelines, the assessment should be done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience. The persons assessing the application should be independent of the sponsor, the clinical trial site, and the investigators involved, as well as free from any other undue influence.

(19) The assessment of applications for the authorisation of clinical trials should be conducted on the basis of appropriate expertise. Specific 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.

(20) In practice, sponsors do not always have all the information needed for submitting a complete application for authorisation of a clinical trial in all of the Member States where a clinical trial is eventually going to be conducted. It should be possible for sponsors to submit an application solely on the basis of documents assessed jointly by those Member States where the clinical trial might be conducted.

(21) The sponsor should be allowed to withdraw the application for authorisation of a clinical trial. To ensure the reliable functioning of the assessment procedure, however, an application for authorisation of a clinical trial should be withdrawn only for the entire clinical trial. It should be possible for the sponsor to submit a new application for authorisation of a clinical trial following the withdrawal of an application.

(22) In practice, in order to reach recruitment targets or for other reasons, sponsors may have an interest in extending the clinical trial to an additional Member States after the initial authorisation of the clinical trial. An authorisation mechanism should be provided to allow for such extension, while avoiding the re-assessment of the application by all

the Member States concerned which were involved in the initial authorisation of the clinical trial.

(23) Clinical trials are usually subject to many modifications after they have been authorised. Those modifications may relate to the conduct, the design, the methodology, the investigational or auxiliary medicinal product, or the investigator or clinical trial site involved. Where those modifications have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial, they should be subject to an authorisation procedure similar to the initial authorisation procedure.

(24) The content of the application dossier for authorisation of a clinical trial should be harmonised in order to ensure that all Member States have the same information available and to simplify the application process for clinical trials.

(25) In order to increase transparency in the area of clinical trials, data from a clinical trial should only be submitted in support of a clinical trial application if that clinical trial has been recorded in a publicly accessible and free of charge database which is a primary or partner registry of, or a data provider to, the international clinical trials registry platform of the World Health Organization (WHO ICTRP). Data providers to the WHO ICTRP create and manage clinical trial records in a manner that is consistent with the WHO registry criteria. Specific provision should be made for data from clinical trials started before the date of application of this Regulation.

(26) It should be left to Member States to establish the language requirements for the application dossier. To ensure that the assessment of the application for authorisation of a clinical trial functions smoothly, Member States should consider accepting a commonly understood language in the medical field as the language for the documentation not destined for the subject.

(27) 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. Directive 2001/20/EC contains an extensive set of rules for the protection of subjects. These rules should be upheld. Regarding the rules concerning the determination of the legally designated representatives of incapacitated persons and minors, those rules diverge in Member States. It should therefore be left to Member States to determine the legally designated representatives of incapacitated persons and minors. Incapacitated subjects, minors, pregnant women and breastfeeding women require specific protection measures.

(28) An appropriately qualified medical doctor or, where appropriate, a qualified dental practitioner should be responsible for all medical care provided to the subject, including the medical care provided by other medical staff.

(29) It is appropriate that universities and other research institutions, under certain circumstances that are in accordance with the applicable law on data protection, be able to collect data from clinical trials to be used for future scientific research, for example for medical, natural or social sciences research purposes. In order to collect data for

such purposes it is necessary that the subject gives consent to use his or her data outside the protocol of the clinical trial and has the right to withdraw that consent at any time. It is also necessary that research projects based on such data be made subject to reviews that are appropriate for research on human data, for example on ethical aspects, before being conducted.

(30) In accordance with international guidelines, the informed consent of a subject should be in writing. When the subject is unable to write, it may be recorded through appropriate alternative means, for instance through audio or video recorders. Prior to obtaining informed consent, the potential subject should receive information in a prior interview in a language which is easily understood by him or her. The subject should have the opportunity to ask questions at any moment. Adequate time should be provided for the subject to consider his or her decision. In view of the fact that in certain Member States the only person qualified under national law to perform an interview with a potential subject is a medical doctor while in other Member States this is done by other professionals, it is appropriate to provide that the prior interview with a potential subject should be performed by a member of the investigating team qualified for this task under the national law of the Member State where the recruitment takes place.

(31) In 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.

(32) This Regulation should be without prejudice to national law requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, should himself or herself assent in order to participate in a clinical trial.

(33) It is appropriate to allow that informed consent be obtained by simplified means for certain clinical trials where the methodology of the trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products. In those clinical trials the investigational medicinal products are used in accordance with the marketing authorisations, and the individual subject receives a standard treatment regardless of whether he or she accepts or refuses to participate in the clinical trial, or withdraws from it, so that the only consequence of non-participation is that data relating to him or her are not used for the clinical trial. Such clinical trials, which serve to compare established treatments, should always be conducted within a single Member State.

(34) Specific provisions should be defined for the protection of pregnant and breastfeeding women participating in clinical trials and in particular when the clinical trial does not have the potential to produce results of direct benefit to her or to her embryo, foetus or child after birth.

(35) Persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, and persons, who

due to their age, disability or state of health are reliant on care and for that reason accommodated in residential care institutions, that is accommodations providing an uninterrupted assistance for persons who necessitate such assistance, are in a situation of subordination or factual dependency and therefore may require specific protective measures. Member States should be allowed to maintain such additional measures.

(36) This Regulation should provide for clear rules concerning informed consent in emergency situations. Such situations relate to cases where for example a patient has suffered a sudden life-threatening medical condition due to multiple traumas, strokes or heart attacks, necessitating immediate medical intervention. For such cases, intervention within an ongoing clinical trial, which has already been approved, may be pertinent. However, in certain emergency situations, it is not possible to obtain informed consent prior to the intervention. This Regulation should therefore set clear rules whereby such patients may be enrolled in the clinical trial under very strict conditions. In addition, the said clinical trial should relate directly to the medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative. Any previously expressed objection by the patient should be respected, and informed consent from the subject or from his or her legally designated representative should be sought as soon as possible.

(37) In order to allow patients to assess possibilities to participate in a clinical trial, and to allow for effective supervision of a clinical trial by the Member State concerned, the start of the clinical trial, the end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified. In accordance with international standards, the results of the clinical trial should be reported within one year from the end of the clinical trial.

(38) The date of the first act of recruitment of a potential subject is the date on which the first act of the recruitment strategy described in the protocol was performed, e. g. the date of a contact with a potential subject or the date of the publication of an advertisement for a particular clinical trial.

(39) The sponsor should submit a summary of the results of the clinical trial together with a summary that is understandable to a layperson, and the clinical study report, where applicable, within the defined timelines. Where it is not possible to submit the summary of the results within the defined timelines for scientific reasons, for example when the clinical trial is still ongoing in third countries and data from that part of the trial are not available, which makes a statistical analysis not relevant, the sponsor should justify this in the protocol and specify when the results are going to be submitted.

(40) In order for the sponsor to assess all potentially relevant safety information, the investigator should, as a rule, report to him all serious adverse events.

(41) The sponsor should assess the information received from the investigator, and report safety information on serious adverse events which are suspected unexpected serious adverse reactions to the European Medicines Agency (‘the Agency’).

(42) The Agency should forward that information to the Member States for them to assess it.

(43) The members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have agreed on a detailed set of guidelines on good clinical practice which is an internationally accepted standard for designing, conducting, recording and reporting clinical trials, consistent with principles that have their origin in the World Medical Association's Declaration of Helsinki. When designing, conducting, recording and reporting clinical trials, detailed questions may arise as to the appropriate quality standard. In such a case, the ICH guidelines on good clinical practice should be taken appropriately into account for the application of the rules set out in this Regulation, provided that there is no other specific guidance issued by the Commission and that those guidelines are compatible with this Regulation.

(44) The conduct of a clinical trial should be adequately monitored by the sponsor in order to ensure the reliability and robustness of the results. Monitoring may also contribute to subject safety, taking into account the characteristics of the clinical trial and respect for fundamental rights of subjects. When establishing the extent of monitoring, the characteristics of the clinical trial should be taken into account.

(45) The individuals involved in conducting a clinical trial, in particular investigators and other healthcare professionals, should be sufficiently qualified to perform their tasks, and the facilities where a clinical trial is to be conducted should be suitable for that clinical trial.

(46) In order to ensure subject safety and the reliability and robustness of data from clinical trials, it is appropriate to provide that there should be arrangements for traceability, storage, return and destruction of investigational medicinal products, depending on the nature of the clinical trial. For the same reasons, there should also be such arrangements for unauthorised auxiliary medicinal products.

(47) During a clinical trial, a sponsor may become aware of serious breaches of the rules for the conduct of that clinical trial. This should be reported to the Member States concerned in order for action to be taken by those Member States, where necessary.

(48) Apart from the reporting of suspected unexpected serious adverse reactions, there may be other events which are relevant in terms of benefit-risk balance and which should be reported in a timely manner to the Member States concerned. It is important for subject safety that, in addition to serious adverse events and reactions, all unexpected events that might materially influence the benefit-risk assessment of the medicinal product or that would lead to changes in the administration of a medicinal product or in overall conduct of a clinical trial are notified to the Member States concerned. Examples of such unexpected events include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as carcinogenicity).

(49) Where unexpected events require an urgent modification of a clinical trial, it should be possible for the sponsor and the investigator to take urgent safety measures without awaiting prior authorisation. If such measures constitute a temporary halt of the clinical

trial, the sponsor should apply for a substantial modification before restarting the clinical trial.

(50) In order to ensure compliance of the conduct of a clinical trial with the protocol, and in order for investigators to be informed about the investigational medicinal products they administer, the sponsor should supply the investigators with an investigator's brochure.

(51) The information generated in a clinical trial should be recorded, handled and stored adequately for the purpose of ensuring subject rights and safety, the robustness and reliability of the data generated in the clinical trial, accurate reporting and interpretation, effective monitoring by the sponsor and effective inspection by Member States.

(52) In order to be able to demonstrate compliance with the protocol and with this Regulation, a clinical trial master file, containing relevant documentation to allow effective supervision (monitoring by the sponsor and inspection by Member States), should be kept by the sponsor and by the investigator. The clinical trial master file should be archived appropriately to allow for supervision after the clinical trial has ended.

(53) Where there are problems with respect to the availability of authorised auxiliary medicinal products, unauthorised auxiliary medicinal products may be used in a clinical trial in justified cases. The price of the authorised auxiliary medicinal product should not be considered as having an effect on the availability of such medicinal products.

(54) Medicinal products intended for research and development trials fall outside the scope of Directive 2001/83/EC of the European Parliament and of the Council[(5)]. Such medicinal products include medicinal products used in the context of a clinical trial. They should be covered by specific rules taking account of their peculiarities. In establishing these rules, a distinction should be made between investigational medicinal products (the tested product and its reference products, including placebos) and auxiliary medicinal products (medicinal products used in the context of a clinical trial but not as investigational medicinal products), such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess end-points in a clinical trial. Auxiliary medicinal products should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial.

(55) In order to ensure subject safety and the reliability and robustness of data generated in a clinical trial, and in order to allow for the distribution of investigational and auxiliary medicinal products to clinical trial sites throughout the Union, rules on the manufacturing and import of both investigational and auxiliary medicinal products should be established. As is already the case for Directive 2001/20/EC, those rules should reflect the existing rules of good manufacturing practices for products covered by Directive 2001/83/EC. In some specific cases, it should be possible to allow deviations from those rules in order to facilitate the conduct of a clinical trial. Therefore, the applicable rules should allow for some flexibility, provided that subject safety, as well as reliability and robustness of the data generated in the clinical trial are not compromised.

(56) The requirement to hold an authorisation for manufacture or import of investigational medicinal products should not apply to the preparation of investigational radiopharmaceuticals from radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions for use in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State.

(57) Investigational and auxiliary medicinal products should be appropriately labelled in order to ensure subject safety and the reliability and robustness of data generated in clinical trials, and in order to allow for the distribution of those products to clinical trial sites throughout the Union. The rules for labelling should be adapted to the risks to subject safety and the reliability and robustness of data generated in clinical trials. Where the investigational or auxiliary medicinal product have already been placed on the market as an authorised medicinal product in accordance with Directive 2001/83/EC and Regulation (EC) No 726/2004 of the European Parliament and of the Council[(6)], as a general rule no additional labelling should be required for clinical trials that do not involve the blinding of the label. Moreover, there are specific products, such as radiopharmaceuticals used as diagnostic investigational medicinal product, where the general rules on labelling are inappropriate in view of the very controlled setting of the use of radiopharmaceuticals in clinical trials.

(58) In order to ensure clear responsibilities, the concept of a ‘sponsor’ of a clinical trial, in line with international guidelines, was introduced by Directive 2001/20/EC. This concept should be upheld.

(59) In practice, there may be loose, informal networks of researchers or research institutions which jointly conduct a clinical trial. Those networks should be able to be co-sponsors of a clinical trial. In order not to weaken the concept of responsibility in a clinical trial, where a clinical trial has several sponsors, they should all be subject to the obligations of a sponsor under this Regulation. However, the co-sponsors should be able to split up the responsibilities of the sponsor by contractual agreement.

(60) In order to ensure that enforcement action may be taken by Member States and that legal proceedings may be brought in appropriate cases, it is appropriate to provide that sponsors that are not established in the Union should be represented by a legal representative in the Union. However in view of the divergent approaches of the Member States as regards civil and criminal liability, it is appropriate to leave to each Member State concerned, as regards its territory, the choice as to whether or not to require such a legal representative, provided that at least a contact person is established in the Union.

(61) Where, in the course of a clinical trial, damage caused to the subject leads to the civil or criminal liability of the investigator or the sponsor, the conditions for liability in such cases, including issues of causality and the level of damages and sanctions, should remain governed by national law.

(62) In clinical trials compensation should be ensured for damages successfully claimed in accordance with the applicable laws. Therefore Member States should ensure that

systems for compensation for damages suffered by a subject are in place which are appropriate to the nature and the extent of the risk.

(63) The Member State concerned should be given the power to revoke the authorisation of a clinical trial, suspend a clinical trial or require the sponsor to modify a clinical trial.

(64) In order to ensure compliance with this Regulation, Member States should be able to conduct inspections and should have adequate inspection capacities.

(65) The Commission should be able to control whether Member States correctly supervise compliance with this Regulation. Moreover, the Commission should be able to control whether regulatory systems of third countries ensure compliance with the specific provisions of this Regulation and Directive 2001/83/EC concerning clinical trials conducted in third countries.

(66) In order to streamline and facilitate the flow of information between sponsors and Member States as well as between Member States, the Agency should, in collaboration with Member States and the Commission, set up and maintain an EU database, accessed through an EU portal.

(67) In order to ensure a sufficient level of transparency in the clinical trials, the EU database should contain all relevant information as regards the clinical trial submitted through the EU portal. The EU database should be publicly accessible and data should be presented in an easily searchable format, with related data and documents linked together by the EU trial number and with hyperlinks, for example linking together the summary, the layperson's summary, the protocol and the clinical study report of one clinical trial, as well as linking to data from other clinical trials which used the same investigational medicinal product. All clinical trials should be registered in the EU database prior to being started. As a rule, the start and end dates of the recruitment of subjects should also be published in the EU database. No personal data of data subjects participating in a clinical trial should be recorded in the EU database. The information in the EU database should be public, unless specific reasons require that a piece of information should not be published, in order to protect the right of the individual to private life and the right to the protection of personal data, recognised by Articles 7 and 8 of the Charter. Publicly available information contained in the EU database should contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors.

(68) For the purposes of this Regulation, in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted, the procedure for granting themarketing authorisation has been completed, the application for marketing authorisation has been withdrawn. In addition, the main characteristics of a clinical trial, the conclusion on Part I of the assessment report for the authorisation of a clinical trial, the decision on the authorisation of a clinical trial, the substantial modification of a clinical trial, and the clinical trial results including reasons for temporary halt and early termination, in general, should not be considered confidential.

(69) Within a Member State, there may be several bodies involved in the authorisation of clinical trials. In order to allow for effective and efficient cooperation between Member States, each Member State should designate one contact point.

(70) The authorisation procedure set out in this Regulation is largely controlled by Member States. Nevertheless, the Commission and the Agency should support the good functioning of that procedure, in accordance with this Regulation.

(71) In order to carry out the activities provided for in this Regulation, Member States should be allowed to levy fees. However, Member States should not require multiple payments to different bodies involved in the assessment, in a given Member State, of an application for authorisation of a clinical trial.

(72) In order to ensure uniform conditions for the implementation of this Regulation, implementing powers should be conferred on the Commission in respect of the establishment and modification of rules on cooperation between the Member States when assessing the information provided by the sponsor on the Eudravigilance database and the specification of detailed arrangements for inspection procedures. Those powers should be exercised in accordance with Regulation (EU) No 182/2011 of the European Parliament and of the Council[7].

(73) In order to supplement or amend certain non-essential elements of this Regulation, the power to adopt acts in accordance with Article 290 of the Treaty on the Functioning of the European Union (TFEU) should be delegated to the Commission in respect of: the amendment of Annexes I, II, IV and V to this Regulation in order to adapt them to technical progress or to take account of international regulatory developments in which the Union or the Member States are involved, in the field of clinical trials; the amendment of Annex III in order to improve the information on the safety of medicinal products, to adapt technical requirements to technical progress or to take account of international regulatory developments in the field of safety requirements in clinical trials endorsed by bodies in which the Union or the Member States participate; the specification of the principles and guidelines of good manufacturing practice and the detailed arrangements for inspection for ensuring the quality of investigational medicinal products; the amendment of Annex VI in order to ensure subject safety and the reliability and robustness of data generated in a clinical trial or to take account of technical progress. It is of particular importance that the Commission carry out appropriate consultations during its preparatory work, including at expert level. The Commission, when preparing and drawing-up delegated acts, should ensure a simultaneous, timely and appropriate transmission of relevant documents to the European Parliament and to the Council.

(74) Directive 2001/83/EC provides that that Directive does not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products as abortifacients. Directive 2001/83/EC provides that national legislation prohibiting or restricting the use of any specific type of human or animal cells is not, in principle, affected by either that Directive or any of the Regulations referred to therein. Likewise, this Regulation should not affect national law prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal

products used as abortifacients. In addition, this Regulation should not affect national law prohibiting or restricting the sale, supply or use of medicinal products containing narcotic substances within the meaning of the relevant international conventions in force such as the Single Convention on Narcotic Drugs of 1961 of the United Nations. Member States should communicate those national provisions to the Commission.

(75) Directive 2001/20/EC provides that no gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity. It is appropriate to maintain that provision.

(76) Directive 95/46/EC of the European Parliament and of the Council[(8)] applies to the processing of personal data carried out in the Member States within the framework of this Regulation, under the supervision of the Member States competent authorities, in particular the public independent authorities designated by the Member States and Regulation (EC) No 45/2001 of the European Parliament and of the Council[(9)] applies to the processing of personal data carried out by the Commission and the Agency within the framework of this Regulation, under the supervision of the European Data Protection Supervisor. Those instruments strengthen personal data protection rights, encompassing the right to access, rectification and withdrawal, as well as specify the situations when restriction on those rights may be imposed. With a view to respecting those rights, while safeguarding the robustness and reliability of data from clinical trials used for scientific purposes and the safety of subjects participating in clinical trials, it is appropriate to provide that, without prejudice to Directive 95/46/EC, the withdrawal of informed consent should not affect the results of activities already carried out, such as the storage and use of data obtained on the basis of informed consent before withdrawal.

(77) Subjects should not have to pay for investigational medicinal products, auxiliary medicinal products, medical devices used for their administration and procedures specifically required by the protocol, unless the law of the Member State concerned provides otherwise.

(78) The authorisation procedure set out in this Regulation should apply as soon as possible, in order for sponsors to reap the benefits of a streamlined authorisation procedure. However, in view of the importance of the extensive IT functionalities required for the authorisation procedure, it is appropriate to provide that this Regulation should only become applicable once it has been verified that the EU portal and the EU database are fully functional.

(79) Directive 2001/20/EC should be repealed to ensure that only one set of rules applies to the conduct of clinical trials in the Union. In order to facilitate the transition to the rules set out in this Regulation, sponsors should be allowed to start and conduct a clinical trial in accordance with Directive 2001/20/EC during a transitional period.

(80) This Regulation is in line with the major international guidance documents on clinical trials, such as the 2008 version of the World Medical Association's Declaration of Helsinki and good clinical practice, which has its origins in the Declaration of Helsinki.

(81) As regards Directive 2001/20/EC, experience also shows that a large proportion of clinical trials are conducted by non-commercial sponsors. Non-commercial sponsors

frequently rely on funding which comes partly or entirely from public funds or charities. In order to maximise the valuable contribution of such non-commercial sponsors and to further stimulate their research but without compromising the quality of clinical trials, measures should be taken by Member States to encourage clinical trials conducted by those sponsors.

(82) This Regulation is based on the double legal basis of Articles 114 and 168(4)(c) TFEU. It aims at achieving an internal market as regards clinical trials and medicinal products for human use, taking as a base a high level of protection of health. At the same time, this Regulation sets high standards of quality and safety for medicinal products in order to meet common safety concerns as regards these products. Both objectives are being pursued simultaneously. These two objectives are inseparably linked and one is not secondary to another. Regarding Article 114 TFEU, this Regulation harmonises the rules for the conduct of clinical trials in the Union, therefore ensuring the functioning of the internal market in view of the conduct of a clinical trial in several Member States, the acceptability throughout the Union of data generated in a clinical trial and submitted in the application for the authorisation of another clinical trial or of the placing on the market of a medicinal product, and the free movement of medicinal products used in the context of a clinical trial. Regarding Article 168(4)(c) TFEU, this Regulation sets high standards of quality and safety for medicinal products by ensuring that data generated in clinical trials are reliable and robust, thus ensuring that treatments and medicines which are intended to be an improvement of a treatment of patients build on reliable and robust data. Moreover, this Regulation sets high standards of quality and safety of medicinal products used in the context of a clinical trial, thus ensuring the safety of subjects in a clinical trial.

(83) This Regulation respects the fundamental rights and observes the principles recognised in particular by the Charter and notably human dignity, the integrity of the person, the rights of the child, respect for private and family life, the protection of personal data and the freedom of art and science. This Regulation should be applied by the Member States in accordance with those rights and principles.

(84) The European Data Protection Supervisor has given an opinion[(10)] pursuant to Article 28(2) of Regulation (EC) No 45/2001.

(85) Since the objective of this Regulation, namely to ensure that, throughout the Union, clinical trial data are reliable and robust while ensuring respect for the rights, safety, dignity and well-being of subjects, cannot be sufficiently achieved by the Member States but can rather, by reason of its scale, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union. In accordance with the principle of proportionality, as set out in that Article, this Regulation does not go beyond what is necessary in order to achieve that objective,

HAVE ADOPTED THIS REGULATION:

(**1**) OJ C 44, 15.2.2013, p. 99.

(**2**) Position of the European Parliament of 3 April 2014 (not yet published in the Official Journal) and decision of the Council of 14 April 2014.

(**3**) 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 (OJ L 121, 1.5.2001, p. 34).

(**4**) Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p. 1).

(**5**) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

(**6**) Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1.)

(**7**) Regulation (EU) No 182/2011 of the European Parliament and of the Council of 16 February 2011 laying down the rules and general principles concerning mechanisms for control by Member States of the Commission's exercise of implementing powers (OJ L 55, 28.2.2011, p. 13).

(**8**) Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (OJ L 281, 23.11.1995, p. 31).

(**9**) Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data (OJ L 8, 12.1.2001, p. 1).

(**10**) OJ C 253, 3.9.2013, p. 10.

Changes to legislation:
There are currently no known outstanding effects for the Regulation (EU) No 536/2014 of the European Parliament and of the Council, Introductory Text.