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| Subject: | Proposal for a Regulation of the European Parliament and of the Council on Clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC |

Delegations will find in the Annex to this Note the consolidated text of the draft regulation as approved today by the Permanent Representatives Committee (Part 1).

**ANNEX**

2012/0192 (COD)

Proposal for a

**REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL**

**on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC**

(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 Commission[1],

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

Having regard to the opinion of the European Economic and Social Committee[2],

Having regard to the opinion of the Committee of the Regions[3],

~~***After consulting the European data Protection Supervisor,***~~ [4]

Acting in accordance with the ordinary legislative procedure[5],

Whereas:

(1) In a clinical trial the ***rights,*** safety***, dignity and well-being*** ~~***and rights***~~ 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.

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1 OJ C , , p. .

2 OJ C , , p. .

3 OJ C , , p. .

4 ~~***XXX.***~~

5 OJ C , , p. .

(3) The existing definition of a clinical trial as contained in 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[6] 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 EU legislation governing medicinal products, which builds on the dichotomy of 'clinical trial' and 'non-interventional study'.

(4) Directive 2001/20/EC aimed to simplify and harmonise the administrative provisions governing clinical trials in the European 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 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 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 submission procedures, the multiple submission of largely identical information should be avoided and replaced by the submission of one application dossier through a single submission portal to all the Member States concerned. ***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 the single European portal.***

6 OJ L 121, 1.5.2001, p. 34.

(5) Experience with Directive 2001/20/EC ~~has~~ also ***indicates that*** ~~shown that the aim of simplifying and harmonising the administrative provisions governing clinical trials in the Union cannot be achieved in the legal form of a Directive but can only be achieved with the legal form of a Regulation. Only~~ the legal form of a Regulation ~~ensures that the Member States base their assessment of an application for authorisation of a clinical trial on identical criteria, rather than on diverging national transposition measures. This holds not only for the entire authorisation process, but also for all other issues addressed in this Regulation, such as safety reporting during clinical trials, and the requirements for labelling of the medicinal products used in the context of a clinical trial~~ ***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, ~~***nor ethical aspects of a clinical trial,***~~ such as informed consent.

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

(8) The timelines for assessing an application dossier for clinical trials should be sufficiently long to assess the file, while 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.

***(8a) Clinical research for the development of orphan medicinal products as defined in Regulation (EC) 141/2000 and 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.***

***(8b) Member States should assess with efficiency and within the given timelines all clinical trials applications. 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, like in the case of rare and ultra rare diseases.***

(9) 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 in particular the case where the investigational medicinal product is covered by a marketing authorisation (i.e. the quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure) ***or its use is an evidence based treatment supported by published scientific evidence on safety and efficacy*** and where 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 to assess standard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health. They should be subject to less stringent rules, ***as regards monitoring of the clinical trials, requirements for the contents of the master file and traceability of investigational medicinal products*** ~~***such as shorter deadlines for approval***~~***. 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 authorization 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.***

***(9a) The OECD Council Recommendation on the Governance of Clinical Trials of 10 December 2012 introduced different categories for clinical trials. Those categories are compatible with the ones of this Regulation as the OECD Categories A and B(1) correspond to the definition of a low-intervention clinical trial, and the OECD Categories B(2) and C correspond to the definition of a clinical trial under this Regulation.***

(10) 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 inconveniences for the subject. Regarding the relevance, numerous aspects should be taken into account, including whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products ***and whether the surrogate end points, when they are used, are justified***.

***(10a) The subjects participating in a clinical trial should represent the population groups (e.g. gender and age groups) that are likely to use the medicinal product investigated in the clinical trial unless otherwise justified in the protocol.***

***(10b) 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 requirements related to their specific characteristics and the protection of their health and well-being.***

***(10c) Experience with Directive 2001/20/EC has also shown that a large part of clinical trials are conducted by non-commercial sponsors. Non-commercial sponsors frequently rely on funding which partly or entirely comes from the public funds or charities. In order to maximize the use of their valuable contribution and to further stimulate their research but without any discrimination towards the quality of trials, measures should be taken by Member States to encourage trials conducted by non-commercial sponsors.***

(11) The authorisation procedure should provide for the possibility to ***extend*** ~~***suspend***~~ the assessment in order to allow the sponsor to address questions or comments raised during the assessment of the application dossier. ~~***The maximum duration of the suspension should reflect whether the clinical trial is a low-intervention clinical trial or not.***~~ Moreover, it should be ensured that, following the end of the ***extension*** ~~***suspension***~~, there is always sufficient time for assessing the additional information submitted.

~~***(12) Some aspects in a clinical trial application relate to issues of an intrinsic national nature or to ethical aspects of a clinical trial. Those issues should not be assessed in cooperation among all Member States concerned.***~~

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

(14) It should be left to the Member State concerned to determine the appropriate body or bodies to be involved in this assessment ***and to organise the involvement of the ethics committees within the timeframes for the authorisation of the clinical trial set out in this regulation***. ~~***This***~~ ***These*** decision***s are*** ~~***is***~~ a matter of internal organisation of each Member State. Member States, when determining the appropriate body or bodies, should ensure the involvement of lay persons and patients. They should also ensure that the necessary expertise is available. In any case, however, and 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 from the sponsor, the ~~***institution of the***~~ trial site, and the investigators involved, as well as free of any other undue influence.

***(14a) 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 situation, minors, incapacitated subjects, pregnant and breastfeeding women and, where appropriate, other identified specific population groups, like elderly people or people suffering from rare and ultra rare diseases.***

(15) In practice, when submitting an application for authorisation of a clinical trial, sponsors do not always have full certainty about 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 the documents assessed jointly by those Member States where the clinical trial might be conducted.

(16) 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.

(17) In practice, in order to reach recruitment targets or for other reasons, sponsors may have an interest to extend 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 this 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.

(18) Clinical trials are usually subject to many modifications after they have been authorised. Those modifications may relate to the conduct, design, methodology, investigational or auxiliary medicinal product, or the investigator or 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.

(19) 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.

(20) In order to increase transparency in the area of clinical trials, clinical trial data submitted in support of a clinical trial application should be based only on clinical trials recorded in a publicly accessible ***and free of charge*** database. ***Clinical trial data based on clinical trials conducted before the date of application of this Regulation should be registered in a public register which is a primary or partnered registry of the international clinical trials registry platform of the World Health Organisation. Specific provisions should be provided for data based on clinical trials conducted before the date of application of this Regulation.***

***(20a) For the purposes of this regulation in general the data included into clinical study reports should not be considered commercially confidential once a marketing authorisation has been granted, the decision-making process on the application for a marketing authorisation has been completed, or an application for marketing authorisation has been withdrawn. In addition, the main characteristics of the clinical trial, the conclusion on Part I and the decision on the authorisation of the clinical trial, the substantial modification of the clinical trial, and the clinical trial results including reasons for temporary halt and early termination, in general should not be considered confidential.***

(21) 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 to the subject.

(22) The human dignity and right to the integrity of the person are recognized in the Charter of Fundamental rights of the European Union. 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 contained an extensive set of rules for the protection of subjects. These rules should be upheld. Regarding the rules concerning the determination of the legal***ly designated*** representative of incapacitated persons and minors, those rules diverge in Member States. It should therefore be left to Member States to determine the legal***ly designated*** representative of incapacitated persons and minors. ***Incapacitated subjects, minors, pregnant and breastfeeding women require specific protection measures.***

***(22a) An appropriately qualified medical doctor or, where appropriate, a qualified dental practitioner should be responsible for all medical care administered to the subject, including the medical care administered by other medical staff.***

(23) 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*** ~~***circumstances***~~, ***such as for example*** ~~***due to***~~ the unconsciousness of the patient and the absence of an immediately available legal***ly designated*** representative, it is not possible to obtain informed consent prior to the intervention. The 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 which causes the impossibility of the patient to give informed consent. Any previously expressed objection by the patient must be respected, and informed consent from the subject or the legal***ly designated*** representative should be sought as soon as possible.

(24) In accordance with international guidelines, the ~~***free and***~~ informed consent of ~~***the***~~ ***a*** subject should be in writing~~***, save in exceptional situations***~~***. When the subject is unable to write, it may be recorded through appropriate alternative means (for instance through audio or video recorders).*** ~~***It should be based on information which is clear, relevant and understandable to the subject.***~~

***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 national law in the Member State where the recruitment takes place.***

***(24a) 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 the situation of institutional or hierarchical dependency that could inappropriately influence her or his decision to participate.***

***(24b) This Regulation should be without prejudice to national legislation requiring that a minor who is capable of forming an opinion and assessing the information given to him or her, should, in addition to the informed consent given by the legally designated representative, himself or herself agree to the participation in order to take part in a clinical trial.***

***(24ba) 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 individual 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 the same treatment regardless if 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 from her or him 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.***

***(24c) 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.***

***(24d) Persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision cannot take part in a 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 (i.e. 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.***

(25) 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 recruitment 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 to the competent authorities within one year of the end of the clinical trial.

***(25aa) It is appropriate that universities and other research institutions should 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 e.g. for medical, natural or social sciences research purposes. In order to collect data for such purposes it is necessary that the subject gives her/his 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 being based on such data could be made subject to reviews appropriate for research on human data e.g. on ethical aspects before being conducted.***

***(25a) The date of the first act of recruitment is the date on which the first act following 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.***

***(25b) The sponsor should submit a summary of the results of the clinical trial together with the layperson summary, and the clinical study report where applicable, within the defined time-lines. Where it is not possible to submit the summary of the results within the defined time-lines due to scientific reasons (e.g., when the clinical trial is still ongoing in third countries and data from that part of the trial are not available making therefore a statistical analysis not relevant), the sponsor should justify this in the protocol and specify when the results are going to be submitted.***

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

(27) 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 Agency.

(28) The Agency should forward this information to the Member States for them to assess this information.

(29) 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 for good clinical practice which are now 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 used as guidance 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 without prejudice to this Regulation.

(30) 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.

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

(32) ~~***Depending on the circumstances of the clinical trial, it should be possible to trace the investigational and certain auxiliary medicinal products in***~~ ***In*** order to ensure subject safety and ***reliability and*** ~~***data***~~ robustness ***of data*** ~~***and reliability***~~ ***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, ~~***those products***~~ ***there*** should ***also*** be ***such arrangements for unauthorised auxiliary medicinal products*** ~~***destroyed where necessary and, depending on the circumstances of the clinical trial, subject to specific storage conditions***~~.

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

(34) 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 patient safety that in addition to serious adverse events and reactions all other unexpected events that might materially influence the benefit-risk assessment of medicinal product or that would lead to changes in the administration of a medicinal product or in overall conduct of a clinical trial should be 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).***

(35) 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, the sponsor should apply for a substantial modification before restarting the clinical trial.***

(36) In order to ensure compliance of the conduct of the 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.

(37) The information generated in the 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 ~~***or the Commission***~~.

(38) 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 ~~***and the Commission***~~), 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.

***(38a) Where there are problems in 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 to the availability of such medicinal products***.

(39) 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 of 6 November 2001 on the Community code relating to medicinal products for human use[7]. 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, i.e. medications unrelated to the clinical trial and not relevant for the design of the clinical trial.

(40) 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 importation 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.

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7 OJ L 311, 28.11.2001, p. 67.

***(40a) The requirement to hold an authorisation for manufacture or importation 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.***

(41) Investigational and auxiliary medicinal products should be appropriately labelled 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 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 a clinical trial. 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, as a general rule no additional labelling should be required for open-label trials. 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.

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

(43) In practice, there may be loose, informal networks of researchers or research institutions which run jointly 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 ***~~responsibilies~~ responsibilities*** of the sponsor by contractual agreement.

(44) ~~*The sponsor of a clinical trial may be located in a third country. In order to facilitate supervision and control, a sponsor located in a third country should establish a contact person in the Union to allow for the competent authority of the Member State concerned to communicate with the sponsor. That contact person may be a legal or a natural person.*~~ ***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 EU should be represented by a legal representative in the EU. 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 EU.***

(45) 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 legislation.

(46) In clinical trials ~~*with non-authorised investigational medicinal products, or where the intervention poses more than an insignificant risk to subject safety,*~~ 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.***

~~*(47) At present, such damage compensation is provided by way of insurance. This insurance may cover damages to be paid to the subject by the sponsor and investigator in the case of established liability. It may also compensate the subject directly without prior establishment of the liability of the sponsor or investigator. Experience shows that the insurance market is small and costs for insurance coverage are disproportionately high. Moreover, as liability regimes differ widely between Member States, it is difficult and burdensome for the sponsor of a multinational trial to obtain insurance in accordance with those national laws. Therefore, each Member State should establish a national indemnification mechanism which compensates subjects in accordance with the laws of that Member State.*~~

(48) The Member State concerned should be given the power to ***revoke the authorisation*** ~~***early terminate***~~, suspend or ***require the sponsor to*** modify a clinical trial.

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

(50) 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.

(51) In order to streamline and facilitate the flow of information between sponsors and Member States as well as between Member States, the ~~***Commission***~~ ***European Medicines Agency*** should***, in collaboration with Member States and the Commission,*** set up and maintain a database, accessed through a portal.

(52) ***In order to ensure a sufficient level of transparency in the clinical trials, ~~T~~the*** database should contain all relevant information as regards the clinical trial ***submitted through the EU portal. The 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 hyperlinks, for example linking together the summary, the layperson's summary, the protocol and the Clinical Study Report of one 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 database prior to being started. The start and end dates of the recruitment of subjects should also be published in the database***. No personal data of data subjects participating in a clinical trial should be recorded in the database. The information in the 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 of Fundamental Rights of the European Union. ***Publicly available information contained in the database should contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors.***

(53) 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.

(54) The authorisation procedure set up in this Regulation is largely controlled by Member States. Nevertheless, the Commission should support the good functioning of this procedure, in accordance with this Regulation.

(55) 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 assessing, in a given Member State, an application for authorisation of a clinical trial.

(56) In order to ensure uniform conditions for the implementation of this Regulation, implementing powers should be conferred on the Commission ~~***to adopt implementing acts in relation to inspections***~~. Those powers should be exercised in accordance with 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.

(57) In order to ~~***ensure that information and documentation submitted in an application for authorisation of a clinical trial or a substantial modification allows assessment of the application in view of technical progress and global regulatory requirements, and in order to ensure a high level of subject protection and reliability and robustness of data generated in a clinical trial through a well-functioning safety reporting process and through detailed requirements for manufacturing and labelling of medicinal products used in the context of a clinical trial, the Commission should be empowered***~~ ***supplement or amend certain non-essential elements of this Regulation, the power*** to adopt delegated acts in accordance with Article 290 of the Treaty on the Functioning of the European Union ~~***to amend the list of documentation and information to be submitted in an application for authorisation of a clinical trial or a substantial modification, to amend technical aspects for safety reporting in the context of a clinical trial, to adopt detailed requirements of good manufacturing practice, and to amend the list of information to appear on the labelling of medicinal products used in the context of a clinical trial***~~ ***should be delegated to the Commission***. 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 Council.

(58) ***Article 4(4) of Directive 2001/83/EC provides that this directive should not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products as abortifacients.*** Article 4(5) of Directive 2001/83/EC provides that national legislation prohibiting or restricting the use of any specific type of human or animal cells should, in principle, not be affected by that Directive and all the Regulations referred to therein. Likewise, this Regulation should not affect national legislation prohibiting or restricting the use of any specific type of human or animal cells***, or medicinal products used as abortifacients, as well as medicinal products containing narcotic substances within the meaning of the relevant international conventions in force such as the UN Single Convention 1961***. As in Directive 2001/83/EC, Member States should communicate those national provisions to the Commission.

***Article 9(6) of 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 this provision.***

(59) 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[8] applies to the processing of personal data carried out in the Member States, 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 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[9], which 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 the rights to protection of private data, encompassing the right to access, rectification and withdrawal, as well as specify the situations when restriction on this rights may be imposed.***

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8 OJ L 281, 23.11.1995, p. 31.

9 OJ L 8, 12.1.2001, p. 1.

***With a view to respecting the rights to personal data protection, 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 consent should not affect the results of activities carried out such as the storage and use of data obtained based on consent before withdrawal.***

(60) ~~***Without prejudice to the national systems for the cost and reimbursement of medical treatments, s***~~***S***ubjects 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 national legislation in the Member State concerned provides otherwise***.

(61) The authorisation procedure set up in this Regulation should apply as soon as possible, in order for sponsors to reap the benefits of a streamlined authorisation procedure. However, in ~~***order to allow the setting up at Union level of***~~ ***view of the importance of*** the extensive IT functionalities required for the authorisation procedure, it is appropriate to provide ***that the present Regulation will only become applicable once it has been verified that the EU portal and the EU database are fully functional*** ~~***for a reasonable period to elapse before this Regulation applies***~~.

(62) 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.

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

(64) 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 to meet common safety concerns as regards these products. Both objectives are being pursued simultaneously. Both 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 EU 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 the quality and safety of medicinal products by ensuring that data generated in clinical trials is reliable and robust, thus ensuring that treatments and medicines which are supposed 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.

(65) This Regulation respects the fundamental rights and observes the principles recognised in particular by the Charter of Fundamental Rights of the European Union 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.

***(65a) The European Data Protection Supervisor has given an opinion pursuant to Article 28(2) of 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[10].***

[10] ***OJ L 8, 12.1.2001, p. 1.***

(66) Since the objective of this Regulation, namely to ensure that, throughout the Union, clinical trial data are reliable and robust while ensuring the ***rights,*** safety***, dignity*** and ***well-being*** ~~***rights***~~ of subjects, cannot sufficiently be achieved by the Member States and can, by reason of the scale of the measure, 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:

## Chapter I
## General provisions

*Article 1*

*Scope*

This Regulation shall apply to ***all*** clinical trials conducted in the Union.

It shall not apply to non-interventional studies.

*Article 2*

*Definitions*

For the purposes of this Regulation, the definitions of "medicinal product", "radiopharmaceutical", "adverse reaction", "serious adverse reaction", "immediate packaging" and "outer packaging" in Article 1(2), (6), (11), (12), (23) and (24) of Directive 2001/83/EC shall apply.

The following definitions shall also apply:

(1) 'Clinical study': any investigation in relation to humans intended

(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;

(b) to identify any adverse reactions to one or more medicinal products; or

(c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products;

with the objective of ascertaining their safety or efficacy.

(2) 'Clinical trial': a clinical study which fulfils any of the following conditions:

~~***(a) the investigational medicinal products are not authorised;***~~

~~***(b) according to the protocol of the clinical study, the investigational medicinal products are not used in accordance with the terms of the marketing authorisation of the Member State concerned;***~~

(c) 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;

(d) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study;

(e) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

(3) 'Low-intervention clinical trial': a clinical trial which fulfils all of the following conditions:

(a) the investigational medicinal products***, excluding placebos,*** are authorised;

(b) according to the protocol of the clinical trial,

- the investigational medicinal products are used in accordance with the terms of the marketing authorisation or ~~***their***~~
- ***the*** use ***of the investigational medicinal products*** is ***evidence based*** ~~***a standard treatment***~~ ***and supported by published scientific evidence on safety and efficacy***

in any of the Member States concerned

(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

(4) ‘Non-interventional study’: a clinical study other than a clinical trial;

(5) ‘Investigational medicinal product’: a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial;

(6) 'Normal clinical practice': the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder;

(7) ‘Advanced therapy investigational medicinal product’: an investigational medicinal product which is an advanced therapy medicinal product as defined in Article 2(1) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council[11];

(8) ‘Auxiliary medicinal product’: a medicinal product used ***for the needs*** ~~***in the context***~~ of a clinical trial ***as described in the protocol***, but not as an investigational medicinal product;

(9) ‘Authorised investigational medicinal product’: a medicinal product authorised in accordance with Regulation (EC) No 726/2004, or, in any Member State concerned, in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product;

(10) 'Authorised auxiliary medicinal product’: a medicinal product authorised in accordance with Regulation (EC) No 726/2004, or, in any Member State concerned, in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an auxiliary medicinal product;

***(10a) ‘ethics committee’: an independent body in a Member State established in accordance with national law and empowered to give opinions for the purposes of this Regulation, taking into account the views of lay-persons, in particular patients or patients organisations;***

[11] OJ L 324, 10.12.2007, p. 121.

(11) ‘Member State concerned’: the Member State where an application for authorisation of a clinical trial or of a substantial modification has been submitted under Chapters II and III of this Regulation;

(12) ‘Substantial modification’: any change to any aspect of the clinical trial which is made after notification of the decision referred to in Articles 8, 14, 19, 20 and 23 and which is likely to 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;

(13) ‘Sponsor: an individual, company, institution or organisation which takes responsibility for the initiation**.** ***~~and~~*** management ***and setting up the financing*** of the clinical trial;

(14) ‘Investigator: an individual responsible for the conduct of a clinical trial at a clinical trial site;

***(14a) ‘Principal investigator’: an investigator who is the responsible leader of a team of investigators that conduct the clinical trial at a clinical trial site;***

(15) ‘Subject’: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control;

(16) ‘Minor’: a subject who is, according to the laws of the Member State concerned, under the age of legal competence to give informed consent;

(17) ‘Incapacitated subject’: a subject who is, for other reasons than the age of legal competence to give informed consent, ***~~legally~~*** incapable of giving informed consent according to the laws of the Member State concerned;

(18) ‘Legal***ly designated*** representative’: a natural or legal person, authority or body which, according to the national law of the Member State concerned, ***is empowered to*** give***~~s~~*** informed consent ***~~for~~ on behalf of*** a subject who is incapacitated or a minor;

(19) 'Informed consent': a process by which a subject ***freely and*** voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate ***or, in case of minors and incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the trial***;

(20) 'Protocol': a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial***. The term protocol encompasses successive versions of the protocol and protocol amendments***;

***(20a) 'Investigator's brochure': a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects;***

(21) 'Manufacturing': total and partial manufacture, as well as the various processes of dividing up, packaging, labelling (including blinding);

(22) 'Start of the clinical trial': the first act of recruitment of a potential subject ***for a specific clinical trial***, unless defined differently in the protocol;

(23) 'End of the clinical trial': the last visit of the last subject, ~~***unless***~~ ***or at a later time as*** defined ~~***differently***~~ in the protocol;

***(23a) 'Early termination of the clinical trial': the premature end of the clinical trial due to any reason before the conditions specified in the protocol are complied with;***

(24) 'Temporary halt of the clinical trial': ***an*** interruption ***not provided in the protocol*** of the conduct of a clinical trial by the sponsor with the intention of the sponsor to resume it;

(25) 'Suspension of the clinical trial': interruption of the conduct of a clinical trial by a Member State;

(26) ‘Good clinical practice’: a set of detailed ethical and scientific quality requirements for designing, conducting, performing, monitoring, auditing, recording, analysing and reporting clinical trials ensuring that the rights, safety and well-being of subjects are protected, and that the data generated in the clinical trial are reliable and robust;

(27) ‘Inspection’: the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect;

(28) ‘Adverse event’: any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment;

(29) ‘Serious adverse event’: any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect, is life-threatening or results in death;

(30) ‘Unexpected serious adverse reaction’: a serious adverse reaction the nature, severity or outcome of which is not consistent with the reference safety information.

***(30a) 'Clinical study report': a report on the clinical trial presented in an easily searchable format, prepared in accordance with Annex I, Part I, Module 5 of 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 and submitted in a marketing authorisation application.***

For the purposes of this Regulation, a subject who falls under the definition of both “minor” and “incapacitated subject” shall be considered as an incapacitated subject.

*Article 3*

*General principle*

A clinical trial may be conducted only if

– the rights, safety***, dignity*** and well-being of subjects are protected ***and prevail over all other interests***;

and

– ~~***the data***~~ ***it is designed to*** generate~~***d in the clinical trial are going to be***~~ reliable and robust ***data***.

## Chapter II

## Authorisation procedure for a clinical trial

*Article 4*

*Prior authorisation*

A clinical trial shall be subject to ***scientific and ethical review and be authorised*** ~~***authorisation***~~ in accordance with this ***Regulation*** ~~***Chapter***~~. ***The ethical review shall be performed by an independent ethics committee in accordance with the Member State national legislation. The review by the independent ethics committee may encompass aspects related to Part I as per Article 6 and Part II as per Article 7 thereof as appropriate for each Member State concerned.***

***Member State shall ensure that the timelines for the review by the independent ethics committees are aligned with the timelines and procedures set out in this Regulation for the assessment of the application for authorisation of a clinical trial.***

*Article 5*

*Submission of an application*

1. In order to obtain an authorisation, the sponsor shall submit an application dossier to the intended Member States concerned through the portal referred to in Article 77 (hereinafter 'EU portal').

The sponsor shall propose one of the Member States concerned as reporting Member State.

***~~Where~~ If another Member State concerned is willing to be a reporting Member State or where*** the proposed reporting Member State does not wish to be the reporting Member State, ***~~it shall agree with another Member State concerned that the latter will be the reporting Member State. If no Member State concerned accepts to be the reporting Member State, the proposed reporting Member State shall be the reporting Member State~~ this shall be notified through the EU portal to Member States concerned not later than 3 days after the application is submitted***.

***If only one Member State concerned is willing to be the reporting Member State or if the clinical trial involves only one Member State, it shall be the reporting Member State. If there is no Member State or there is more than one Member State willing to be the reporting Member State, the reporting Member State shall be selected by an agreement among the Member States concerned taking into account the recommendations referred to in paragraph 2 of Article 81.***

***If there is no agreement among the Member States concerned, the proposed reporting Member State shall be the reporting Member State.***

***The reporting Member State shall notify the sponsor and the Member States concerned that it is the reporting Member State through the EU portal within 6 days after the submission of the application.***

***1a. The sponsor shall, when the application is for a low-intervention clinical trial where the investigational medicinal product is not used in accordance with the terms of the marketing authorisation but the use is an evidence based and supported by published scientific evidence on safety and efficacy propose one of the Member States concerned, where its use is evidence-based treatment as reporting Member State.***

2. Within ~~***six***~~ ***ten*** days following submission of the application dossier, the ~~***proposed***~~ reporting Member State shall ***validate the application taking into account considerations expressed by the Member States concerned and*** notify the sponsor through the EU portal of the following:

   ~~***(a) whether it is the reporting Member State or which other Member State concerned is the reporting Member State;***~~

   (b) whether the clinical trial falls within the scope of this Regulation;

   (c) whether the application is complete in accordance with Annex I;

   ~~***(d) whether the clinical trial is a low-intervention clinical trial, where claimed by the sponsor***~~.

   ***Member States concerned may communicate to the reporting Member State any considerations relevant to the validation of the application within seven days following the submission of the application dossier.***

3. Where the ~~***proposed***~~ reporting Member State has not notified the sponsor within the time period referred to in paragraph 2, the clinical trial applied for shall be considered as falling within the scope of this Regulation~~***, and***~~ the application shall be considered complete~~***, the clinical trial shall be considered a low-intervention clinical trial if this is claimed by the sponsor, and the proposed reporting Member State shall be the reporting Member State***~~.

4. Where the ~~***proposed***~~ reporting Member State***, taking into account considerations expressed by the Member States concerned,*** finds that the application is not complete, ***or*** that the clinical trial applied for does not fall within the scope of this Regulation~~***, or that the clinical trial is not a low-intervention clinical trial while this is claimed by the sponsor***~~, it shall inform the sponsor thereof through the EU portal and shall set a maximum of ~~***six***~~ ***ten*** days for the sponsor to comment or to complete the application through the EU portal.

***Within five days following receipt of the comments or the completed application the reporting Member State shall notify the sponsor according to the points (b) and (c) of paragraph 2.***

~~***Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be considered as withdrawn.***~~

Where the ~~proposed~~ reporting Member State has not notified the sponsor ~~***according to points (a) to (d) of paragraph 2 within three days following receipt of the comments or of the completed application***~~ ***within the time period referred to in the second subparagraph***, the application shall be considered complete~~***,***~~ ***and*** the clinical trial shall be considered as falling within the scope of this Regulation~~***, the clinical trial shall be considered as a low-intervention clinical trial if this is claimed by the sponsor, and the proposed reporting Member State shall be the reporting Member State***~~.

***Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be deemed to have lapsed.***

5. For the purposes of this Chapter, the date on which the sponsor is notified in accordance with paragraph 2 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the time periods referred to in paragraphs 2 and 4.

*Article 6*

*Assessment report – Aspects covered by Part I*

1. The reporting Member State shall assess the application with regard to the following aspects:

***(aa) Whether the clinical trial is a low-intervention clinical trial, where claimed by the sponsor.***

(a) Compliance with Chapter V with respect to the following:

(i) The anticipated therapeutic and public health benefits taking account of all of the following:

– the characteristics of and knowledge about the investigational medicinal products;

– the relevance of the clinical trial, ***including whether the groups of subjects participating in the clinical trial represent the population to be treated, or if not, explanation and justification is provided in accordance with Annex I, point 13, sixth indent, and*** taking account of the current state of scientific knowledge, and of whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products***, and, where applicable, an opinion formed by the Paediatric Committee on a paediatric investigation plan in accordance with Regulation (EC) No 1901/2006***;

– the reliability and robustness of the data generated in the clinical trial, taking account of statistical approaches, design of the trial and methodology (including sample size and randomisation, comparator and endpoints);

(ii) The risks and inconveniences for the subject, taking account of all of the following:

– the characteristics of and knowledge about the investigational medicinal products and the auxiliary medicinal products;

– the characteristics of the intervention compared to normal clinical practice;

– the safety measures, including provisions for risk minimisation measures, monitoring, safety reporting, and the safety plan;

– the risk to subject health posed by the medical condition for which the investigational medicinal product is being investigated;

(b) Compliance with the requirements concerning the manufacturing and importation of investigational medicinal products and auxiliary medicinal products set out in Chapter IX;

(c) Compliance with the labelling requirements set out in Chapter X;

(d) The completeness and adequateness of the investigator's brochure.

2. The reporting Member State shall draw up an assessment report. The assessment of the aspects referred to in paragraph 1 shall constitute Part I of the assessment report.

3. The assessment report shall contain one of the following conclusions concerning the aspects addressed in Part I of the assessment report:
   (a) the conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation;
   (b) the conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion;
   (c) the conduct of the trial is not acceptable in view of the requirements set out in this Regulation.

4. The reporting Member State shall submit ***the final*** Part I of the assessment report ***via the EU portal***, including its conclusion, to the sponsor and to the other Member States concerned within ***45 days from the validation date.*** ~~***the following time periods:***~~
   ~~***(a) within 10 days from the validation date for low-intervention clinical trials;***~~
   ~~***(b) within 25 days from the validation date for clinical trials other than low-intervention clinical trials;***~~
   ~~***(c) within 30 days from the validation date for any clinical trial with an advanced therapy investigational medicinal product.***~~
   ~~***For the purposes of this Chapter, the assessment date shall be the date on which the assessment report is submitted to the sponsor and to the other Member States concerned.***~~

5. ~~***Until the assessment date, any Member State concerned may communicate to the reporting Member State any considerations relevant to the application. The reporting Member State shall take those considerations duly into account.***~~
   ***For clinical trials involving more than one Member State the assessment process shall include three phases:***
   ***(a) an initial assessment phase performed by the reporting Member State within 26 days from the validation date;***
   ***(b) a coordinated review phase performed within 12 days from the end of the initial assessment phase involving all concerned Member States;***

***(c) a consolidation phase performed by the reporting Member State within 7 days from the end of coordinated review phase.***

***During the initial assessment phase the reporting Member State shall develop a draft Part I of the assessment report and circulate it to all concerned Member States.***

***During the coordinated review phase Member States concerned and the reporting Member State shall jointly review the application based on the draft Part I of the assessment report and shall share any considerations relevant to the application.***

***During the consolidation phase the reporting Member State shall take considerations of the Member States concerned duly into account in finalising the Part I of the assessment report and shall record how all have been dealt with. The reporting Member State shall submit the final Part I of the assessment report to the sponsor and all concerned Member States within the time period referred to in paragraph 4.***

***For the purposes of this Chapter, the date on which the final Part I of the assessment report is submitted to the sponsor and to the other Member States concerned shall be the reporting date.***

6. The reporting Member State, and only the reporting Member State, may, between the validation date and the ~~***assessment***~~ ***reporting*** date, request additional ~~***explanations***~~ ***information*** from the sponsor, taking into account the considerations referred to in paragraph 5.

For the purpose of obtaining ~~***those***~~ ***this*** additional ~~***explanations***~~ ***information***, the reporting Member State may ~~***suspend***~~ ***extend*** the time period referred to in paragraph 4 for a maximum of ~~***10***~~ ***31*** days ~~***for low-intervention clinical trials and for a maximum of 20 days for trials other than low-intervention clinical trials***~~.

***The sponsor shall submit the requested additional information within 12 days from the receipt of the request.***

***Upon ~~Where, upon~~*** receipt of the additional ***~~explanations~~ information, the concerned Member States together with the reporting Member State shall jointly review any additional information provided by the sponsor together with the original application and shall share any considerations relevant to the application. The coordinated review shall be performed within 12 days from the receipt of additional information and the further consolidation shall be performed within seven days from the end of coordinated review. The reporting Member State shall take considerations of the Member States concerned duly into account in finalising the Part I of the assessment report and shall record how all have been dealt with ~~the remaining time period for submitting Part I of the assessment report is less than three days in the case of low-intervention clinical trials, and less than five days for other than low-intervention clinical trials, it shall be extended to three and five days respectively~~***.

Where the sponsor does not provide additional ***~~explanations~~ information*** within the time period set by the reporting Member State in accordance with the ***third ~~second~~*** subparagraph, the application shall be considered as withdrawn ***in all Member States***.

The request for additional ***~~explanations~~ information*** and the additional ***~~explanations~~ information*** shall be submitted through the EU portal.

***6a. The reporting Member State may also extend the time period referred to in paragraph~~s~~ 4 for a further 50 days for clinical trials involving an advanced therapy medicinal products or medicinal products as defined in point 1 of the Annex to the Regulation (EC) No 726/2004, for the purpose of consulting with experts. In such case time periods referred to in paragraphs 5 and 6 of this Article shall apply*** **mutatis mutandis.**

***~~7. The sponsor may at its own initiative change the content of the application only between the validation date and the assessment date and only for duly justified reasons. In this case, the reporting Member State may, depending on the extent of the change to the content of the application, suspend the period referred to in paragraph 4 for a maximum of 60 days.~~***

*Article 7*

*Assessment report – Aspects covered by Part II*

1. Each Member State concerned shall assess, for its own territory, the application with respect to the following aspects:
   (a) compliance with the requirements for informed consent as set out in Chapter V;
   (b) compliance of the arrangements for rewarding or compensating investigators and subjects with the requirements set out in Chapter V;
   (c) compliance of the arrangements for recruitment of subjects with the requirements set out in Chapter V;
   (d) compliance with Directive 95/46/EC;
   (e) compliance with Article 46;
   (f) compliance with Article 47;
   (g) compliance with Article 72;
   (h) compliance with the applicable rules for the collection, storage and future use of biological samples of the subject.

   The assessment of the aspects referred to in the first subparagraph shall constitute Part II of the assessment report.

2. Each Member State concerned shall complete its assessment within ***~~ten~~ 45*** days from the validation date ***and submit Part II of the assessment report, including its conclusion, to the sponsor***.

   ***Each Member State concerned ~~It~~*** may request, with justified reasons, additional ***~~explanations~~ information*** from the sponsor regarding the aspects referred to in paragraph 1 only within that time period.

3. For the purpose of obtaining additional ***~~explanations~~ information*** from the sponsor, the Member State concerned may ***~~suspend~~ extend*** the period referred to in paragraph 2 for a maximum of ***~~ten~~ 31*** days.

   ***The sponsor shall submit the requested additional information within 12 days from the receipt of the request.***

***Upon receipt of the additional information, the Member State concerned shall complete its assessment within 19 days.***

~~***Where, upon receiving the additional explanations, the remaining time period for completing the assessment referred to in paragraph 1 is less than five days, it shall be extended to five days.***~~

Where the sponsor does not provide additional ~~***explanations***~~ ***information*** within the time period set by the Member State ***concerned*** in accordance with the ~~***first***~~ ***second*** subparagraph, the application shall be considered as withdrawn. The withdrawal shall apply only with respect to the Member State concerned.

The request ***for additional information*** and the additional ~~***explanations***~~ ***information*** shall be submitted through the EU portal.

*Article 8*

*Decision on the clinical trial*

1. Each Member State concerned shall notify the sponsor through the EU Portal as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

   Notification shall be done by way of one single decision within ~~***ten***~~ ***five*** days from the ~~***assessment***~~ ***reporting*** date or the last day of the assessment referred to in Article 7, whichever is later.

   ***An authorisation of a clinical trial subject to conditions is restricted to conditions, which by their nature cannot be fulfilled at the time of the approval.***

2. Where the conclusion as regards Part I of the assessment report of the reporting Member State is that the conduct of the clinical trial is acceptable or acceptable subject to conditions, ***that*** ~~***the***~~ conclusion ~~***of shall be considered as the conclusion of***~~ the Member State concerned ~~***shall be the same as that of the reporting Member State***~~.

Notwithstanding the first subparagraph, a Member State concerned may disagree ***to accept Part I of the assessment report*** ~~***with the conclusion of the reporting Member State***~~ only on the following grounds:

(a) ~~***significant differences in normal clinical practice between the Member State concerned and the reporting Member State which***~~ ***when it considers that participation in the clinical trial*** would lead to a subject receiving an inferior treatment than in normal clinical practice ***in this Member State***;

(b) infringement of the national legislation referred to in Article 86***;***

***(c) disagreement with the conclusion of the reporting Member State based on safety and data reliability and robustness considerations submitted under paragraph 5 or 6 of Article 6.***

Where the Member State concerned disagrees with the conclusion on the basis of ~~***point (a) of***~~ the second subparagraph, it shall communicate its disagreement, together with a detailed justification ~~***based on scientific and socio-economic arguments, and a summary thereof,***~~ through the EU portal to the Commission, to all Member States, and to the sponsor.

3. Where, regarding Part I of the assessment report, the clinical trial is acceptable or acceptable subject to conditions, the Member State concerned shall include in its decision its conclusion on Part II of the assessment report.

***3a. A concerned Member State shall refuse to approve a clinical trial if it disagrees with Part I of the assessment report of the reporting Member State on any of the grounds referred to in the second subparagraph of paragraph 2 of this Article, or finds, on duly justified grounds, that the aspects listed in Article 7, paragraph 1, are not complied with or where an ethics committee has issued a negative opinion which in accordance with national law is valid for the entire Member State.***

***3b. Where the conclusion as regards Part I of the assessment report of the reporting Member State is negative that conclusion shall be considered as the conclusion of the Member State concerned.***

***3c. The Member State shall provide for an appeal procedure for the decision referred to in paragraph 3a.***

4. Where the Member State concerned has not notified the sponsor of its decision within the time periods referred to in paragraph 1, the conclusion on Part I of the assessment report shall be considered as the decision of the Member State concerned on the application for authorisation of the clinical trial.

5. The Member States concerned shall not request additional ***information regarding the Part 1 assessment*** ~~***explanations***~~ from the sponsor after the ~~***assessment***~~ ***reporting*** date.

6. For the purposes of this Chapter, the notification date shall be the date on which the decision referred to in paragraph 1 is notified to the sponsor. Where the sponsor has not been notified in accordance with paragraph 1, the notification date shall be the last day of the time period provided for in paragraph 1.

***7. If within two years after the date of authorisation no subject has been included in the clinical trial in a concerned Member State, the authorisation expires in this Member State unless an extension on request of the sponsor has been approved following the procedure referred to in Chapter III.***

*Article 9*

*Persons assessing the application*

1. Member States shall ensure that the persons validating and assessing the application do not have conflicts of interest, are independent of the sponsor, ~~***the institution***~~ of the trial site and the investigators involved ***and persons financing the clinical trial***, as well as free of any other undue influence.

***In order to guarantee independence and transparency, the Member States shall ensure that persons admitting and assessing Parts I and II of the application have no financial or personal interests which could affect their impartiality. These persons shall make an annual declaration of their financial interests.***

2. Member States shall ensure that the assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience.

3. ***At least one layperson shall participate in*** ~~***In***~~ the assessment~~***, the view of at least one person whose primary area of interest is non-scientific shall be taken into account. The view of at least one patient shall be taken into account***~~.

*Article 10*

*Specific considerations for vulnerable populations*

1. Where the subjects are minors, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of paediatric expertise or after taking advice on clinical, ethical and psychosocial problems in the field of paediatrics.

2. Where the subjects are incapacitated, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of expertise in the relevant disease and the patient population concerned or after taking advice on clinical, ethical and psychosocial questions in the field of the relevant disease and the patient population concerned.

***2a. Where the subjects are pregnant or breastfeeding women, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of expertise in the relevant condition and the population represented by the subject concerned.***

***2b. If according to the protocol the clinical trial provides for the participations of specific groups or sub-groups of subjects, where appropriate, specific consideration shall be given to the assessment of the application for authorisation of the clinical trial on the basis of expertise in the population represented by the subjects concerned.***

3. In ***any*** applications for authorisation of ***a*** clinical trials referred to in Article 32, specific consideration shall be given to the circumstances of the conduct of the clinical trial.

*Article 11*

*Submission and assessment of applications limited to aspects covered by Part I of the assessment report*

Where the sponsor so requests, the application for authorisation of a clinical trial, its assessment and the ***~~decision~~ conclusion*** shall be limited to the aspects covered by Part I of the assessment report.

After the notification of the ***~~decision~~ conclusion*** on the aspects covered by Part I of the assessment report, the sponsor may ***within two years*** apply for an authorisation limited to aspects covered by Part II of the assessment report. ***In that application the sponsor shall declare that he is not aware of any new substantial scientific information that would change the validity of any item submitted in the initial application.*** In this case, that application shall be assessed in accordance with Article 7 and the Member State concerned shall notify its decision ***on the clinical trial ~~with regard to Part II of the assessment report~~*** in accordance with Article 8. ***If the sponsor does not apply for an authorisation limited to aspects covered by Part II of the assessment report within two years, the application shall be deemed to have lapsed.***

*Article 12*

*Withdrawal*

The sponsor may withdraw the application at any time until the ***~~assessment~~ reporting*** date. In such a case, the application may only be withdrawn with respect to all Member States concerned. ***The reasons for the withdrawal shall be communicated through the EU portal.***

*Article 13*

*Resubmission*

This Chapter is without prejudice to the possibility for the sponsor to submit, following the refusal to grant an authorisation or the withdrawal of an application, an application for authorisation to any intended Member State concerned. That application shall be considered as a new application for authorisation of another clinical trial.

*Article 14*

*Subsequent addition of a Member State concerned*

1. Where the sponsor wishes to extend an authorised clinical trial to another Member State (hereinafter 'additional Member State concerned'), the sponsor shall submit an application dossier to that Member State through the EU portal.

   The application may be submitted only after the notification date of the initial authorisation decision.

2. The reporting Member State for the application referred to in paragraph 1 shall be the reporting Member State for the initial authorisation procedure.

3. The additional Member State concerned shall notify the sponsor through the EU portal by way of one single decision as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether the authorisation is refused within ***52 days.*** ~~***the following time periods:***~~

   ~~***(a) 25 days from the date of submission of the application referred to in paragraph 1 for low-intervention clinical trials;***~~

   ~~***(b) 35 days from the date of submission of the application referred to in paragraph 1 for clinical trials other than low-intervention clinical trials;***~~

   ~~***(c) 40 days from the date of submission of the application referred to in paragraph 1 for any clinical trial with an advanced therapy investigational medicinal product.***~~

   ***An authorisation of a clinical trial subject to conditions is restricted to conditions, which by their nature cannot be fulfilled at the time of the approval.***

4. Where the conclusion as regards Part I of the assessment report of the reporting Member State is that the conduct of the clinical trial is acceptable or acceptable subject to conditions, ***that conclusion shall be considered as*** the conclusion of the additional Member State concerned ~~***shall be the same as that of the reporting Member State referred to in Article 6(3)***~~.

Notwithstanding the first subparagraph, an additional Member State concerned may disagree ***to accept Part I of the assessment report*** ~~***with the conclusion of the reporting Member State***~~ only on the following grounds:

(a) ~~***significant differences in normal clinical practice between the Member State concerned and the reporting Member State which***~~ ***when it considers that participation in the clinical trial*** would lead to a subject receiving an inferior treatment than in normal clinical practice ***in this Member State***;

(b) infringement of the national legislation referred to in Article 86~~.~~***;***

***(c) disagreement with the conclusion of the reporting Member State based on safety and data reliability and robustness considerations submitted under paragraph 5 or 6 of this Article.***

Where the additional Member State concerned disagrees with the conclusion on the basis of ~~***point (a) of***~~ the second subparagraph, it shall communicate its disagreement, together with a detailed justification ~~***based on scientific and socio-economic arguments, and a summary thereof,***~~ through the EU portal to the Commission, to all Member States, and to the sponsor.

5. Between the date of submission of the application referred to in paragraph 1 and the expiry of the relevant time period referred to in paragraph 3, the additional Member State concerned may communicate to the reporting Member State ***and other Member States concerned*** any considerations relevant to the application ***through the EU portal***.

6. The reporting Member State, and only the reporting Member State, may, between the date of submission of the application referred to in paragraph 1 and the expiry of the relevant time period referred to in paragraph 3, request additional ***information*** ~~***explanations***~~ from the sponsor concerning Part I of the assessment report, taking into account the considerations referred to in paragraph 5.

For the purpose of obtaining ~~***those***~~ ***this*** additional ~~***explanations***~~ ***information***, the reporting Member State may ~~***suspend***~~ ***extend*** the relevant time period referred to in paragraph 3 for a maximum of ~~***10***~~ ***31*** ~~***days for low-intervention clinical trials and for a maximum of 20 days for trials other than low-intervention clinical trials***~~.

***The sponsor shall submit the requested additional information within 12 days from the receipt of the request.***

***Upon ~~Where, upon~~*** receipt of the additional ***~~explanations~~ information, ~~the remaining time period for notifying the decision referred to in paragraph 4 is less than three days in the case of low-intervention clinical trials, and less than five days for other than low-intervention clinical trials, it shall be extended to three and five days respectively the~~ additional Member State together with other Member States concerned and the reporting Member State shall jointly review any additional information provided by the sponsor together with the original application and shall share any considerations relevant to the application. The coordinated review shall be performed within 12 days from the receipt of additional information and the further consolidation shall be performed within seven days from the end of coordinated review. The reporting Member State shall take considerations of the Member States concerned duly into account and shall record how all have been dealt with***.

Where the sponsor does not provide additional ***~~explanations~~ information*** within the time period set by the reporting Member State in accordance with the ***~~second~~ third*** subparagraph, the application shall be considered as withdrawn.

The request ***for additional information*** and the additional ***~~explanations~~ information*** shall be submitted through the EU portal.

7. The additional Member State concerned shall assess, for its territory, the aspects relating to Part II of the assessment report within ***~~ten days of the date of submission of the application~~ the time period*** referred to in paragraph ***~~13~~***. Within this time period it may request, with justified reasons, additional ***~~explanations~~ information*** from the sponsor regarding aspects relating to Part II of the assessment report as far as its territory is concerned.

8. For the purpose of obtaining the additional ~~*explanations*~~ ***information from the sponsor***, the additional Member State concerned may ~~***suspend***~~ ***extend*** the period referred to in paragraph 7 for a maximum of ~~***ten***~~ ***31*** days. ~~***Where, upon receipt of the additional explanations, the remaining time period for assessing the aspects relating to Part II of the assessment report is less than five days, it shall be extended to five days.***~~

***The sponsor shall submit the requested additional information within 12 days from the receipt of the request.***

***Upon receipt of the additional information, the Member State concerned shall complete its assessment within 19 days.***

***Where the sponsor does not provide additional information within the time period set by the additional Member State concerned in accordance with the second subparagraph, the application shall be considered as withdrawn. The withdrawal shall apply only with respect to the additional Member State concerned.***

The request for additional ~~***explanations***~~ ***information*** and the additional ~~***explanations***~~ ***information*** shall be submitted through the EU portal.

9. Where, regarding Part I of the assessment report, the clinical trial is acceptable or acceptable subject to conditions, the additional Member State concerned shall include in its decision its conclusion on Part II of the assessment report.

***9a. The additional Member State concerned shall refuse to approve the clinical trial if it disagrees to accept Part I of the assessment report of the reporting Member State on grounds referred to in second subparagraph of paragraph 4 of this Article or finds on duly justified grounds that the aspects relating to Part II of the assessment report are not complied with or where an ethics committee has issued a negative opinion which, in accordance with national law, is valid for the entire Member State.***

10. Where the additional Member State concerned has not notified the sponsor of its decision within the relevant time period referred to in paragraph 3, the conclusion on Part I of the assessment report shall be considered as the decision of the additional Member State concerned on the application for authorisation of the clinical trial.

11. A sponsor shall not submit an application in accordance with this Article where a procedure referred to in Chapter III as regards that clinical trial is pending.

## Chapter III

## Authorisation procedure for a substantial modification of a clinical trial

*Article 15*

*General principles*

A substantial modification***, including the addition of a clinical trial site or change of a principal investigator in the clinical trial site,*** may only be implemented if it has been approved in accordance with the procedure set out in this Chapter.

*Article 16*

*Submission of application*

In order to obtain an authorisation, the sponsor shall submit an application dossier to the Member States concerned through the EU portal.

*Article 17*

*Validation of an application for authorisation of a substantial modification of an aspect covered by Part I of the assessment report*

1. The reporting Member State for the authorisation of a substantial modification shall be the reporting Member State for the initial authorisation procedure.

2. Within ***six*** ~~***four***~~ days following submission of the application dossier, the reporting Member State shall ***validate the application taking into account considerations expressed by the Member States concerned and*** notify the sponsor through the EU portal of the following:

   (a) whether the substantial modification concerns an aspect covered by Part I of the assessment report;

   (b) whether the application is complete in accordance with Annex II~~;~~

   ~~***(c) where the clinical trial is a low-intervention clinical trial, whether it will remain a low-intervention clinical trial after its substantial modification***~~.

   ***Member States concerned may communicate to the reporting Member State any considerations relevant to the validation of the application within 5 days following the submission of the application dossier.***

3. Where the reporting Member State has not notified the sponsor within the time period referred to in paragraph 2, the substantial modification applied for shall be considered as concerning an aspect covered by Part I of the assessment report~~***,***~~ ***and*** the application shall be considered as complete ~~***and, where the clinical trial is a low-intervention clinical trial, it shall be considered as remaining a low-intervention clinical trial after its substantial modification***~~.

4. Where the reporting Member State***, taking into account considerations expressed by the Member States concerned,*** finds that the application does not concern an aspect covered by Part I of the assessment report~~***,***~~ ***or*** that the application is not complete, ~~***or that the clinical trial will no longer be a low-intervention clinical trial after the substantial modification, contrary to what the sponsor claims,***~~ it shall inform the sponsor thereof through the EU portal and shall set a maximum of ~~***six***~~ ***ten*** days for the sponsor to comment or to complete the application through the EU portal.

   ***Within five days following receipt of the comments or the completed application, the reporting Member State shall notify the sponsor according to paragraph 2.***

   ~~***Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be considered as withdrawn.***~~

Where the reporting Member State has not notified the sponsor ***within the time period referred to in the second subparagraph*** ~~***according to points (a) to (c) of paragraph 2 within three days following receipt of the comments or of the completed application***~~***, the substantial modification applied for shall be considered as concerning an aspect covered by Part I of the assessment report and*** the application shall be considered complete ~~***and, where the clinical trial is a low-intervention clinical trial, that it will remain a low-intervention clinical trial after its substantial modification***~~.

***Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be deemed to have lapsed.***

5. For the purposes of Articles 18, 19 and 22, the date on which the sponsor is notified in accordance with paragraph 2 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the time periods referred to in paragraphs 2 and 4.

*Article 18*

*Assessment of a substantial modification of an aspect covered by Part I of the assessment report*

1. The reporting Member State shall assess the application ***with regard to an aspect covered by Part I of the assessment report, including whether the clinical trial will remain a low-intervention clinical trial after its substantial modification*** and draw up an assessment report.

2. The assessment report shall contain one of the following conclusions concerning the aspects addressed in Part I of the assessment report:
   (a) the substantial modification is acceptable in view of the requirements set out in this Regulation;
   (b) the substantial modification is acceptable in view of the requirements set out in this Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion;
   (c) the substantial modification is not acceptable in view of the requirements set out in this Regulation.

3. The reporting Member State shall submit ~~***Part I of***~~ the ***final*** assessment report, including its conclusion, to the sponsor and to the other Member States concerned within ~~***15***~~ ***38*** days from the validation date.

For the purposes of this Article and Articles 19 and 23, the ~~***assessment***~~ ***reporting*** date shall be the date on which the ***final*** assessment report is submitted to the sponsor and to the other Member States concerned.

4. ***For clinical trials involving more than one Member State the assessment process of substantial modification shall include three phases:***

   ***(a) an initial assessment phase performed by the reporting Member State within 19 days from the validation date;***

   ***(b) a coordinated review phase performed within 12 days from the end of the initial assessment phase involving all concerned Member States;***

   ***(c) a consolidation phase performed by the reporting Member State within 7 days from the end of coordinated review phase.***

***During the initial assessment phase the reporting Member State shall develop a draft assessment report and circulate it to all concerned Member States.***

***During the coordinated review phase Member States concerned and the reporting Member State shall jointly review the application based on the draft assessment report and shall share any considerations relevant to the application.***

***During the consolidation phase the reporting Member State shall take considerations of the Member States concerned duly into account in finalising the assessment report and shall record how all have been dealt with. The reporting Member State shall submit the final assessment report to the sponsor and all concerned Member States by the reporting date.***

~~***Until the assessment date, any Member State concerned may communicate to the reporting Member State any considerations relevant to the application. The reporting Member State shall take those considerations duly into account.***~~

5. The reporting Member State, and only the reporting Member State, may, between the validation date and the ~~*assessment*~~ ***reporting*** date, request additional ~~*explanations*~~ ***information*** from the sponsor, taking into account the considerations referred to in paragraph 4.

For the purpose of obtaining ~~*those*~~ ***this*** additional ~~*explanations*~~ ***information***, the reporting Member State may ~~*suspend*~~ ***extend*** the period referred to in paragraph ~~*4*~~ ***3*** for a maximum of ~~*10*~~ ***31*** days.

***The sponsor shall submit the requested additional information within 12 days from the receipt of the request.***

~~*Where, u*~~***U***pon receipt of the additional ~~*explanations*~~ ***information, the concerned Member States together with the reporting Member State shall jointly review any additional information provided by the sponsor together with the original application and shall share any considerations relevant to the application. The coordinated review shall be performed within 12 days from the receipt of additional information and the further consolidation shall be performed within seven days from the end of the coordinated review. The reporting Member State shall take considerations of the Member States concerned duly into account in finalising the assessment report and shall record how all have been dealt with*** ~~*the remaining time period for submitting Part I of the assessment report is less than five days, it shall be extended to five days*~~.

Where the sponsor does not provide additional ~~*explanations*~~ ***information*** within the time period determined by the reporting Member State in accordance with the ~~*second*~~ ***third*** subparagraph, the application shall be considered as withdrawn ***in all Member States concerned***.

The request ***for additional information*** and the additional ~~*explanations*~~ ***information*** shall be submitted through the EU portal.

***5a. The reporting Member State may also extend the time period referred to in paragraph 3 for a further 50 days for clinical trials involving an advanced therapy medicinal products or medicinal products as defined in point 1 of the Annex to the Regulation (EC) No 726/2004, for the purpose of consulting with experts. In such case time periods referred to in paragraphs 4 and 5 of this Article shall apply*** **mutatis mutandis.**

~~***6. The sponsor may at its own initiative change the content of the application only between the validation date and the assessment date and only for duly justified reasons. In this case, the reporting Member State may, depending on the extent of the change to the content of the application, suspend the period referred to in paragraph 3 for up to 60 days.***~~

*Article 19*

*Decision on the substantial modification of an aspect covered by Part I of the assessment report*

1. Each Member State concerned shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

   Notification shall be done by way of one single decision within ~~***ten***~~ ***five*** days from the ~~***assessment***~~ ***reporting*** date.

   ***An authorisation of a substantial modification subject to conditions is restricted to conditions, which by their nature cannot be fulfilled at the time of the approval.***

2. Where the conclusion of the reporting Member State is that the substantial modification is acceptable or acceptable subject to conditions, ~~***the conclusion***~~ ***that conclusion shall be considered as the conclusion*** of the Member State concerned ~~***shall be the same as that of the reporting Member State***~~.

Notwithstanding the first subparagraph, a Member State concerned may disagree with that conclusion of the reporting Member State only on the following grounds:

(a) ~~***significant differences in normal clinical practice between the Member State concerned and the reporting Member State which***~~ ***when it considers that participation in the clinical trial*** would lead to a subject receiving an inferior treatment than in normal clinical practice ***in this Member State***;

(b) infringement of the national legislation referred to in Article 86~~.~~***;***

***(c) disagreement with the conclusion of the reporting Member State based on safety and data reliability and robustness considerations submitted under paragraph 4 or 5 of Article 18.***

Where the Member State concerned disagrees with the conclusion on the basis of ~~***point (a) of***~~ the second subparagraph, it shall communicate its disagreement, together with a detailed justification ~~***based on scientific and socio-economic arguments, and a summary thereof,***~~ through the EU portal to the Commission, to all Member States, and to the sponsor.

***2a. Where the conclusion as regards the substantial modification of aspects covered by Part I of the assessment report of the reporting Member State is negative that conclusion shall be considered as the conclusion of the Member State concerned.***

3. Where the Member State concerned has not notified the sponsor of its decision within the time period referred to in paragraph 1, the conclusion of the assessment report shall be considered as the decision in the Member State concerned on the application for authorisation of the substantial modification.

*Article 20*

*Validation, assessment and decision regarding a substantial modification of an aspect covered by Part II of the assessment report*

1. Within ~~***four***~~ ***six*** days following submission of the application dossier, the Member State concerned shall notify the sponsor through the EU portal of the following:

(a) whether the substantial modification concerns an aspect covered by Part II of the assessment report; and

(b) whether the application is complete in accordance with Annex II.

2. Where the Member State concerned has not notified the sponsor within the time period referred to in paragraph 1 the substantial modification applied for shall be considered as concerning an aspect covered by Part II of the assessment report and the application shall be considered as complete.

3. Where the Member State concerned finds that the substantial modification does not concern an aspect covered by Part II of the assessment report or that the application is not complete, it shall inform the sponsor thereof through the EU portal and shall set a maximum of ~~six~~ **ten** days for the sponsor to comment or to complete the application through the EU portal.

***Within five days following receipt of the comments or the completed application the reporting Member State shall notify the sponsor according to the paragraph 1.***

~~***Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be considered as withdrawn.***~~

Where the Member State concerned has not notified the sponsor ***within the time period referred to in the second subparagraph*** ~~***according to points (a) and (b) of paragraph 1 within three days following receipt of the comments or of the completed application***~~, the substantial modification shall be considered as concerning an aspect covered by Part II of the assessment report and the application shall be considered as complete.

***Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be deemed to have lapsed.***

4. For the purpose of this Article, the date on which the sponsor is notified in accordance with paragraph 1 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the time periods referred to in paragraphs 1 and 3.

5. The Member State concerned shall assess the application and shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of one single decision within ~~*ten*~~ ***38*** days from the validation date.

***An authorisation of a substantial modification subject to conditions is restricted to conditions, which by their nature cannot be fulfilled at the time of the approval.***

6. During the time period referred to in the second subparagraph of paragraph 5 the Member State concerned may request, with justified reasons, additional ~~*explanations*~~ ***information*** from the sponsor regarding the substantial modification as far as its territory is concerned.

For the purpose of obtaining additional ~~***explanations***~~ ***information***, the Member State concerned may ~~***suspend***~~ ***extend*** the time period referred to in the second subparagraph of paragraph 5 for a maximum of ~~***ten***~~ ***31*** days.

***The sponsor shall submit the requested additional information within 12 days from the receipt of the request.***

***Upon receipt of the additional information, the Member State concerned shall complete its assessment within 19 days.***

~~***Where, upon receipt of the additional explanations, the remaining time period for notifying the decision referred to in in the second subparagraph of paragraph 5 is less than five days, it shall be extended to five days.***~~

Where the sponsor does not provide additional ~~***explanations***~~ ***information*** within the time period set by the Member State ***concerned*** in accordance with the ~~***first and second***~~ ***third*** subparagraph, the application shall be considered as withdrawn.

The request ***for additional information*** and the additional ~~***explanations***~~ ***information*** shall be submitted through the EU portal.

***6a. A concerned Member State shall refuse to approve a substantial modification if it finds on duly justified grounds that the aspects covered by the Part II of the assessment report are not complied with or where an ethics committee has issued a negative opinion which in accordance with national law is valid for the entire Member State.***

7. Where the Member State concerned has not notified the sponsor of its decision within the time periods set out in paragraphs 5 and 6, the substantial modification shall be considered as authorised.

*Article 21*

*Substantial modification of aspects covered by Parts I and II of the assessment report*

1. Where a substantial modification relates to aspects covered by Parts I and II of the assessment report, the application for authorisation of that substantial modification shall be validated in accordance with Article 17.

2. The aspects covered by Part I of the assessment report shall be assessed in accordance with Article 18 and the aspects covered by Part II of the assessment report shall be assessed in accordance with Article 22.

*Article 22*

*Assessment of a substantial modification of aspects covered by Parts I and II of the assessment report – Assessment of the aspects covered by Part II of the assessment report*

1. Each Member State concerned shall assess, for its ***own*** territory, the aspects of the substantial modification which are covered by Part II of the assessment report within ~~***ten***~~ ***38*** days from the validation date.

2. During the time period referred to in paragraph 1 the Member State concerned may request, with justified reasons, additional ~~***explanations***~~ ***information*** from the sponsor regarding this substantial modification as far as its territory is concerned.

3. For the purpose of obtaining additional ~~*explanations*~~ ***information*** from the sponsor, the Member State concerned may ~~*suspend*~~ ***extend*** the time period referred to paragraph 1 for a maximum of ~~*ten*~~ ***31*** days.

***The sponsor shall submit the requested additional information within 12 days from the receipt of the request.***

***Upon receipt of the additional information, the Member State concerned shall complete its assessment within 19 days.***

~~*Where, upon receipt of the additional explanations, the remaining time period for the assessment referred to in paragraph 1 is less than five days, it shall be extended to five days.*~~

Where the sponsor does not provide additional ~~*explanations*~~ ***information*** within the time period referred to in the ~~*first and*~~ second subparagraph, the application shall be considered as withdrawn.

The request ***for additional information*** and the additional ~~*explanations*~~ ***information*** shall be submitted through the EU portal.

*Article 23*

*Decision on the substantial modification of aspects covered by Parts I and II of the assessment report*

1. Each Member State concerned shall notify the sponsor through the EU Portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of one single decision within ~~*ten*~~ ***five*** days from the ~~*assessment*~~ ***reporting*** date or the last day of the assessment referred to in Article 22, whichever is later.

***An authorisation of a substantial modification subject to conditions is restricted to conditions, which by their nature cannot be fulfilled at the time of the approval.***

2. Where the conclusion of the reporting Member State is that the substantial modification covered by Part I of the assessment report is acceptable or acceptable subject to conditions, ***~~the~~ that*** conclusion ***shall be considered as the conclusion*** of the Member State concerned ***~~shall be the same as that of the reporting Member State~~***.

   Notwithstanding the first subparagraph, a Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds:

   (a) ***~~significant differences in normal clinical practice between the Member State concerned and the reporting Member State which~~ when it considers that participation in the clinical trial*** would lead to a subject receiving an inferior treatment than in normal clinical practice ***in this Member State***;

   (b) infringement of the national legislation referred to in Article 86~~.~~**;**

   ***(c) disagreement with the conclusion of the reporting Member State based on safety and data reliability and robustness considerations submitted under paragraph 4 or 5 of Article 18.***

   Where the Member State concerned disagrees with the conclusion regarding the substantial modification of aspects covered by Part I of the assessment report on the basis ***~~of point (a) of~~*** the second subparagraph, it shall communicate its disagreement, together with a detailed justification ***~~based on scientific and socio-economic arguments, and a summary thereof,~~*** through the EU portal to the Commission, to all Member States, and to the sponsor.

3. Where, regarding the substantial modification of aspects covered by Part I of the assessment report, the substantial modification is acceptable or acceptable subject to conditions, the Member State concerned shall include in its decision its conclusion on the substantial modification of aspects covered by Part II of the assessment report.

***3a. A concerned Member State shall refuse to approve a substantial modification if it disagrees with Part I of the assessment report of the reporting Member State on grounds referred to in second subparagraph of paragraph 2 of this Article or finds on duly justified grounds that the aspects covered by Part II of the assessment report are not complied with or where an ethics committee has issued a negative opinion which in accordance with national law is valid for the entire Member State.***

***3b. Where the conclusion as regards the substantial modification of aspects covered by Part I of the assessment report of the reporting Member State is negative that conclusion shall be considered as the conclusion of the Member State concerned.***

4. Where the Member State concerned has not notified the sponsor of its decision within the time periods referred to in paragraph 1, the conclusion on the substantial modification of aspects covered by Part I of the assessment report shall be considered as the decision of the Member State concerned on the application for authorisation of the substantial modification.

*Article 24*

*Persons assessing the application*

Article 9 applies to the assessments made under this Chapter.

## Chapter IV
## Application dossier

*Article 25*

*Data submitted in the application dossier*

1. The application dossier for the authorisation of a clinical trial shall contain all ***required*** ~~***the***~~ documentation and information necessary for the validation and assessment referred to in Chapter II and relating to:
   (a) the conduct of the trial, including the scientific context and arrangements taken,
   (b) sponsor, investigators, potential subjects, subjects, and trial sites;

(c) the investigational medicinal products and, where necessary, the auxiliary medicinal products, in particular their properties, labelling, manufacturing and control;

(d) measures to protect subjects~~.~~**;**

***(e) justification why the trial is a low-interventional clinical trial, where claimed by the sponsor.***

The list of documentation and information is set out in Annex I.

2. The application dossier for the authorisation of a substantial modification shall contain all ***required*** ~~***the following***~~ documentation and information necessary for the validation and assessment referred to in Chapter III:

(a) a reference to the clinical trial or clinical trials which are substantially modified ***using the EU trial number***;

(b) a clear description of the substantial modification***, in particular, the nature of and reasons for substantial modification***;

(c) a presentation of data and additional information in support of the substantial modification, where necessary;

(d) a clear description of the consequences of the substantial modification as regards subject right and safety and reliability and robustness of the data generated in the clinical trial.

The list of documentation and information is set out in Annex II.

3. Non-clinical ~~***data***~~ ***information*** submitted in an application dossier shall be based on ***data derived from*** studies complying with Union legislation on the principles of good laboratory practice, as applicable at the time of performance of those studies~~***, or equivalent standards***~~.

4. Where reference is made in the application dossier to data generated in a clinical trial, that clinical trial shall have been conducted in accordance with this Regulation ***or, if conducted prior to the date of application of this Regulation, in accordance with Directive 2001/20/EC***.

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

6. Clinical trial data ***based on clinical trials conducted as from the date referred to in the second paragraph of Article 93 and*** submitted in an application dossier shall be based on clinical trials which have been registered prior to their start in a public register which is a primary ***or partnered*** registry of the international clinical trials registry platform of the World Health Organisation.

***Clinical trial data based on clinical trials conducted before the date referred to in the second paragraph of Article 93 and submitted in an application dossier shall be registered in a public register which is a primary or partnered registry of the international clinical trials registry platform of the World Health Organisation or published in an independent peer-reviewed scientific publication.***

7. Data submitted in an application dossier which do not comply with paragraphs 3 to 6 shall not be considered in the assessment of an application for authorisation of a clinical trial or of a substantial modification.

*Article 26*

*Language requirements*

The language of the application dossier, or parts thereof, shall be determined by the Member State concerned.

Member States, in applying the first paragraph, shall consider accepting, for the documentation not addressed to the subject, a commonly understood language in the medical field.

*Article 27*

*Update by way of delegated acts*

The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to amend Annexes I and II with the objective to adapt them to technical progress or to take account of ***international*** ~~***global***~~ regulatory developments ***in the field of clinical trials***.

## Chapter V
## Protection of subjects and informed consent

*Article 28*

*General rules*

1. A clinical trial may be conducted only where all of the following conditions are met:

(a) the anticipated ***benefits to the subject or*** ~~***therapeutic and***~~ public health ~~***benefits***~~ justify the foreseeable risks and inconveniences ***and compliance with this condition is permanently monitored;***

~~***(b) compliance with point (a) is permanently observed;***~~

***(ba) the subject or, where the subject is not able to give informed consent, his or her legally designated representative has received information in accordance with Article 29(2);***

(c) the subject or, where the subject is not able to give informed consent, his or her legal***ly designated*** representative has given informed consent ***in accordance with Article 29(1)***;

~~***(d) the subject or, where the subject is not able to give informed consent, his or her legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the clinical trial, and the conditions under which it is to be conducted and has also been informed of the right to withdraw from the clinical trial at any time without any resulting detriment;***~~

(e) the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him or her in accordance with Directive 95/46/EC are safeguarded~~.~~***;***

***(ea) the clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subject and both the risk threshold and the degree of distress are specially defined in the protocol and constantly monitored;***

***(eb) the medical care given to subjects is the responsibility of an appropriately qualified medical doctor or, where appropriate, of a qualified dental practitioner;***

***(ec) the subject or, where the subject is not able to give informed consent, his or her legally designated representative, has been provided with contact details of an entity where further information can be received in case of need;***

***(ed) no undue influence including that of a financial nature shall be exerted on subjects to participate in the clinical trial.***

***~~2. The rights, safety and well-being of the subjects shall prevail over the interests of science and society.~~***

***2a. Without prejudice to Directive 95/46/EC, the sponsor may ask the subject at the time when the subject gives his or her informed consent to participate in the clinical trial to consent to use his or her data outside the protocol of the clinical trial exclusively for scientific purposes. That particular consent may be withdrawn at any time by the subject.***

***The scientific research making use of the data outside the protocol of the clinical trial shall be conducted in accordance with applicable legislation on data protection.***

3. Any subject***, or, where the subject is not able to give informed consent, his or her legally designated representative,*** may, without any resulting detriment ***and without having to provide any justification***, withdraw from the clinical trial at any time by revoking his or her informed consent. ***~~The~~ Without prejudice to Directive 95/46/EC, the*** withdrawal of consent shall not affect the activities carried out ***and the use of data obtained*** based on consent before its withdrawal.

*Article 29*

*Informed consent*

1. Informed consent shall be written, dated and signed ~~***and given freely***~~ by the ***person performing the interview and the*** subject or his or her legal***ly designated*** representative after having been duly informed ***in accordance with paragraph 2*** ~~***of the nature, significance, implications and risks of the clinical trial. It shall be appropriately documented***~~. Where the subject is unable to write, ~~***oral***~~ consent ***may be given and recorded through appropriate alternative means*** in the presence of at least one impartial witness ~~***may be given in exceptional cases***~~. ***In that case, the witness shall sign and date the informed consent document.*** The subject or his or her legal***ly designated*** representative shall be provided with a copy of the document ***(or the record)*** by which informed consent has been given. ***The informed consent shall be documented. Adequate time shall be given for the subject to consider his or her decision to participate in the trial.***

2. ***Information*** ~~***Written information***~~ given to the subject and/or the legal***ly 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, benefits, implications, risks and inconveniences of the clinical trial;***
     - ***(ii) the subject' 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 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 subjects participation in the clinical trial;***
     - ***(iv) the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical trial is discontinued; and***
   - ***(b)*** be kept ***comprehensive,*** concise, clear, relevant, and understandable to a lay person ***and;*** ~~***. It shall include both medical and legal information. It shall inform the subject about his or her right to revoke his or her informed consent.***~~
   - ***(c) be provided in a prior interview with a member of the investigating team who is appropriately qualified according to national law of the Member State concerned;***
   - ***(d) include information about the applicable damage compensation regime;***

***(e) include the EU trial number, and information about the availability of the trial results in accordance with paragraph 4.***

***2a. The information referred to in paragraph 2 shall be prepared in writing and be available to the subject or, where the subject is not able to give informed consent, his or her legally designated representative.***

***2b. In the interview, special attention shall be paid to the information needs of individual subjects and specific patient populations, as well as to the methods used to give the information.***

***2c. In the interview, it shall be verified that the subject has understood the information.***

~~***3. The subject shall be provided with a contact point where he or she may obtain further information.***~~

***3a. This Regulation is without prejudice to national legislation requiring that both the signature of the incapacitated person and the signature of the legally designated representative may be required on the informed consent form.***

***3b. This Regulation is without prejudice to national legislation 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, shall also assent in order to participate in a clinical trial.***

***4. The subject shall be informed that the summary of the results of the trial and a summary presented in terms understandable to a layperson will be made available in the EU database pursuant to Article 34(3) irrespective of the trial outcome, and, to the extent possible, when the summaries become available.***

*Article 29a*

*Informed consent in cluster trials*

1. *Where a clinical trial is to be conducted exclusively in one Member State, that Member State may, without prejudice to Article 32, and by way of derogation from Article 28, paragraph 1, points (ba), (c), and (ec), from paragraphs 1, 2(c) and 2a, 2b and 2c of Article 29, and from Article 30 and 31, allow the investigator to obtain informed consent by the simplified means set out in paragraph 2 provided that all of the conditions set out in paragraph 3 are fulfilled.*

2. *For clinical trials that meet the requirements in paragraph 3, informed consent shall be deemed to have been obtained if:*
   - *(a) the information required under Article 29(2(a)), 29(2(b), 29(2(d)) and 29(2(e)) is given in accordance with what is laid down in the protocol prior to the inclusion of the subject in the trial, and this information makes clear, in particular, that the subject can refuse to participate in, or withdraw at any time from, the trial without any resulting detriment;*
   - *(b) the potential subject, after being informed, does not object to participating in the trial.*

3. *Informed consent may be obtained by the simplified means set out in paragraph 2, if all the following conditions are met:*
   - *(aa) the simplified means for obtaining informed consent do not contradict national law in the Member State concerned;*
   - *(a) the methodology of the trial requires that groups of individual subjects rather than individual subjects are allocated to receive different investigational medicinal products in a clinical trial;*
   - *(b) the clinical trial is a low-intervention clinical trial and the investigational medicinal products are used in accordance with the terms of the marketing authorisation;*
   - *(ba) there are no interventions other than the standard treatment of the subjects concerned;*
   - *(c) the protocol justifies the reasons for obtaining informed consent with simplified means and describes the scope of information provided to the subjects, as well as the ways of providing information.*

***4. The investigator shall document all refusals and withdrawals and shall ensure that no data for the clinical trial are collected from subjects that refuse to participate in or have withdrawn from the clinical trial.***

*Article 30*

*Clinical trials on incapacitated subjects*

1. In the case of incapacitated subjects who have not given, or have not refused to give, informed consent before the onset of their incapacity, a clinical trial may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:

   (a) the informed consent of the legal***ly designated*** representative has been obtained***~~,~~ ~~whereby consent shall represent the subject's presumed will~~***;

   (b) the incapacitated subject has received ***~~adequate~~ the*** information ***~~in relation~~ referred to in Article 29(2) adequate*** to his or her capacity ***to ~~for~~*** understand***~~ing~~ it ~~regarding the trial, the risks and the benefits~~***;

   (c) the explicit wish of an incapacitated subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time is ***respected ~~considered~~*** by the investigator;

   (d) no incentives or financial inducements are given ***to the subject or his or her legally designated representative*** except ***for*** compensation for ***expenses and loss of earnings directly related to the*** participation in the clinical trial;

   (e) ***~~such research~~ the clinical trial*** is essential ***with respect to incapacitated subjects ~~to validate~~ and*** data ***of comparable validity cannot be*** obtained in clinical trials on persons able to give informed consent or by other research methods;

   (f) ***~~such research~~ the clinical trial*** relates directly to a ***~~life-threatening or debilitating~~*** medical condition from which the subject suffers;

   ***~~(g) the clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage and both the risk threshold and the degree of distress are specially defined and constantly observed;~~***

(h) there are ***scientific*** grounds for expecting that participation in the clinical trial will produce***:***

***(i)*** a ***direct*** benefit to the incapacitated subject outweighing the risks ***and burdens involved, or***

***(ii) some benefit for the population represented by the incapacitated subjects concerned when the clinical trial relates directly to the life-threatening or debilitating medical condition from which the subject suffers and such trial will pose only minimal risk to, and will impose minimal burden on, the incapacitated subject concerned in comparison with the standard treatment of the incapacitated subject's condition ~~or will produce no risk at all~~***.

***1a. Article 30(1)(h)(ii) shall be without prejudice to more stringent national rules prohibiting the conduct of those clinical trials on incapacitated subjects where there are no scientific grounds to expect that participation in the clinical trial will produce a direct benefit to the subject outweighing the risks and burdens involved.***

2. The subject shall as far as possible take part in the consent procedure.

*Article 31*

*Clinical trials on minors*

1. A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:

(a) the informed consent of the legal***ly designated*** representative has been obtained***~~,~~ ~~whereby consent shall represent the minor's presumed will~~***;

(b) the minor has received ***~~all relevant~~ the*** information ***referred to in Article 29(2)*** in a way adapted to his or her age and ***mental*** maturity, from ***~~professionals~~ the investigators or members of the investigating team*** trained or experienced in working with children***~~,~~ ~~regarding the trial, the risks and the benefits~~***;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time, ***~~is duly taken into consideration~~ respected*** by the investigator ***~~in accordance with his or her age and maturity~~***;

(d) no incentives or financial inducements are given ***to the subject or his or her legally designated representative*** except ***for*** compensation for ***expenses and loss of earnings directly related to the*** participation in the clinical trial;

(e) ~~***such research***~~ ***the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial*** is essential ***with respect to minors*** to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;

(f) ~~***such research***~~ ***the clinical trial*** either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;

~~***(g) the clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage and both the risk threshold and the degree of distress are specially defined and constantly observed;***~~

***(h) there are scientific grounds for expecting that participation in the clinical trial will produce a direct benefit for the minor concerned outweighing the risks and burdens involved or will produce*** some ~~***direct***~~ benefit for the ***population represented by the minor concerned*** ~~***group of patients is obtained from the clinical trial***~~ ***and will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition***.

2. The minor shall take part in the consent procedure in a manner adapted to his or her age and ***mental*** maturity.

***2a. If during a clinical trial the minor reaches the age of majority as defined in the national law of the Member State concerned, his/her express informed consent shall be obtained before the trial may continue.***

*Article 31a*

*Clinical trials on pregnant and breastfeeding women*

***A clinical trial on pregnant and breastfeeding women may be conducted only where, in addition to the conditions set out in Article 28, the following conditions are met:***

***(a) the clinical trial has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth outweighing the risks and burdens involved; or***

***(b) if such clinical trial has no direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth it can be conducted only if:***

***(i) a clinical trial of comparable effectiveness cannot be carried out on women who are not pregnant or breastfeeding;***

***(ii) the clinical trial contributes to the attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, foetuses or children; and***

***(iii) the clinical trial poses a minimal risk to, and imposes a minimal burden on the pregnant or breastfeeding woman concerned, her embryo, foetus or child after birth;***

***(c) where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child;***

***(d) no incentives or financial inducements are given to the subject except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial.***

*Article 31b*

*Additional national measures*

***Member States may maintain additional measures regarding persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision cannot take part in clinical trials, or persons in residential care institutions.***

*Article 32*

*Clinical trials in emergency situations*

1. By way of derogation from points ***(ba) and*** (c) ~~***and (d)***~~ of Article 28(1), from points (a) and (b) of Article 30(1) and from points (a) and (b) of Article 31(1), informed consent ***to participate in a clinical trial*** may be obtained after the ***decision to include the subject in the clinical trial provided that this decision is taken at the time of the first intervention in accordance with the protocol for the clinical trial on a subject*** ~~***start of the clinical trial to continue the clinical trial***~~ and information on the clinical trial ~~***may be***~~ given ***accordingly,*** ~~***after the start of the clinical trial***~~ provided that all of the following conditions are fulfilled:

   (a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, ***the subject is unable*** ~~***it is impossible***~~ to ***provide*** ~~***obtain***~~ prior informed consent ~~***from the subject***~~ and ~~***it is impossible***~~ to ***receive*** ~~***supply***~~ prior information ***on the clinical trial*** ~~***to the subject***~~;

   ***(aa) there are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the trial subject, or the diagnosis of their condition;***

   (b) ~~***no legal representative is available***~~ ***it is not possible within the therapeutic window to supply all prior information and obtain prior informed consent from a legally designated representative of the subject***;

   (c) ***the investigator certifies that he or she is not aware of any objections to participate in the clinical trial*** ~~***the subject has not***~~ previously expressed ***by the subject*** ~~***objections known to the investigator***~~;

   (d) the ***clinical trial*** ~~***research***~~ relates directly to ***the subject's*** ~~***a***~~ medical condition ***because of*** which ~~***causes the impossibility***~~ ***it is not possible within the therapeutic window*** to obtain prior informed consent ***from the subject or from a legally designated representative*** and to supply prior information ***and is of such a nature that it may be conducted exclusively in emergency situations***;

   (e) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject ***in comparison with the standard treatment of the subject's condition***.

2. ***Following an intervention pursuant to paragraph 1, ~~The~~*** informed consent ***in accordance with Article 29 ~~referred to in paragraph 1~~*** shall be ***sought to continue the participation of the subject in the clinical trial ~~obtained~~***, and information on the clinical trial shall be given, in accordance with the following requirements:

(a) regarding incapacitated subjects and minors, the informed consent ***~~referred to in paragraph 1~~*** shall be ***~~obtained as soon as possible~~ sought by the investigator*** from the legal***ly designated*** representative ***without undue delay*** and the information referred to in ***Article 29(2) ~~paragraph 1~~*** shall be given as soon as possible to the subject ***and to the legally designated representative***;

(b) regarding other subjects, the informed consent ***~~referred to in paragraph 1~~*** shall be ***~~obtained as soon as possible~~ sought by the investigator without undue delay*** from the legal***ly designated*** representative or the subject, whichever is sooner and the information referred to in ***Article 29(2) ~~paragraph 1~~*** shall be given as soon as possible to the legal***ly designated*** representative or the subject, whichever is sooner.

For the purposes of point (b), where informed consent has been obtained from the legal***ly designated*** representative, informed consent to continue the ***participation in the clinical*** trial shall be obtained from the subject as soon as ***he or she ~~it~~*** is capable of giving informed consent.

***2a. If the subject or, where applicable, the legal representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the trial.***

## Chapter VI

## Start, end, suspension, temporary halt, and early termination of a clinical trial

*Article 33*

*Notification of the start of the clinical trial and of the end of the recruitment of subjects*

1. The sponsor shall notify each Member State concerned of the start of a clinical trial in relation to that Member State through the EU portal.

   That notification shall be made within 15 days from the start of the clinical trial in relation to that Member State.

***1a. The sponsor shall notify each Member State concerned of the first visit of the first subject in relation to that Member State through the EU portal.***

***That notification shall be made within 15 days from the first visit of the first subject in relation to that Member State.***

2. The sponsor shall notify each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State through the EU portal.

   That notification shall be made within 15 days from the end of the recruitment of subjects. In case of re-start of recruitment, paragraph 1 shall apply.

*Article 34*

*End of the clinical trial,* ***temporary halt and*** *early termination of the clinical trial* ***and submission of the results***

1. The sponsor shall notify each Member State concerned of the end of a clinical trial in relation to that Member State through the EU portal.

   That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State.

***1a. The sponsor shall notify each Member State concerned of the end of a clinical trial in all Member States concerned through the EU portal.***

***That notification shall be made within 15 days from the end of the clinical trial in the last Member State concerned.***

2. The sponsor shall notify each Member State concerned of the end of the clinical trial ***in all Member States concerned and in all third countries concerned*** through the EU portal.

That notification shall be made within 15 days from the end of the clinical trial ***in the last of the Member States and third countries concerned***.

3. ***Irrespective of the outcome of the clinical trial, w~~W~~***ithin one year from the end of a clinical trial ***in all Member States concerned***, the sponsor shall submit to the EU database a summary of the results of the clinical trial.

***It shall be accompanied by a summary written in a manner that is understandable to lay persons.***

***The content of the summary of the results of the clinical trial is set out in Annex IIIa.***

***The content of the summary of the results of the clinical trial for lay persons is set out in Annex IIIb.***

However, where, for scientific reasons ***detailed in the protocol***, it is not possible to submit a summary of the results within one year, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a***~~n~~ justification ~~explanation~~***.

***In addition to the summary of the results, where the trial was intended to be used for obtaining a marketing authorisation for the investigational medicinal product, the applicant for marketing authorisation shall submit to the EU database the clinical study report 30 days after the marketing authorisation has been granted, the decision-making process on an application for a marketing authorisation has been completed, or the applicant for marketing authorisation has withdrawn the application.***

***For cases where the sponsor decides to share raw data on a voluntary basis, the Commission shall produce guidelines for the formatting and sharing of those data.***

***3a. In case of a temporary halt of the clinical trial in all Member States concerned for reasons not affecting the benefit-risk balance, the sponsor shall notify each Member State concerned through the EU portal.***

***That notification shall be made within 15 days from the temporary halt of the clinical trial in all Member States concerned and shall include the reasons for such action.***

***3b. If a temporarily halted clinical trial referred to in paragraph 3a is restarted the sponsor shall notify each Member State concerned through the EU portal.***

***That notification shall be made within 15 days from the restart of the temporarily halted clinical trial in all Member States concerned.***

4. ***If*** ~~***For the purpose of this Regulation, if***~~ ***a*** ~~***suspended or***~~ temporarily halted clinical trial is not restarted ***within two years***, ***the date when this period expires or*** the date of the decision of the sponsor not to restart the clinical trial***, whichever is earlier,*** shall be considered as the end of the clinical trial. In the case of early termination, the date of the early termination shall be considered as the date of the end of the clinical trial.

***In the case of early termination of the clinical trial for reasons not affecting the benefit-risk balance, the sponsor shall notify each Member State concerned through the EU portal of the reasons for such action and, when appropriate, follow-up measures for the subjects.***

5. Without prejudice to paragraph 3, where the clinical trial ***protocol*** provides for a***n*** ~~***primary completion***~~ ***intermediate data analysis*** date prior to the end of the trial, and the respective results of the clinical trial are available, a summary of ~~***those***~~ ***the*** results shall be submitted to the EU database within one year of the ~~***primary completion***~~ ***intermediate data analysis*** date.

*Article 35*

*Temporary halt or early termination by the sponsor for reasons of subject safety*

***1.*** For the purposes of this Regulation, the temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance ***shall be notified to the Member States concerned through the EU portal.***

***That notification shall be made without undue delay but not later than in 15 days from the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures.***

***2.*** ***The*** ~~***and the***~~ restart ***of the clinical trial*** following ~~***such***~~ ***a*** temporary halt ***referred to in paragraph 1*** ~~***of a clinical trial***~~ shall be considered as a substantial modification ***subject to the authorisation procedure laid down in Chapter III*** ~~***of a clinical trial***~~.

***Article 35a***

***Update of the contents of the summary of results and summary for lay persons***

***The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to amend Annexes IIIa and IIIb with the objective to adapt them to technical progress or to take account of international regulatory developments in the field of clinical trials in which the Union or its Member States are involved.***

## Chapter VII

## Safety reporting in the context of a clinical trial

*Article 36*

*Electronic database for safety reporting*

**1.** The European Medicines Agency established by Regulation (EC) No 726/2004 (hereinafter, the "Agency") shall set up and maintain an electronic database for the reporting provided for in Articles 38, and 39. ***That electronic database shall be a module of the database referred to in Article 24 of Regulation (EC) No 726/2004.***

***2. The Agency shall, in collaboration with Member States, develop a standard web-based structured form for the reporting by sponsors to that electronic database of suspected unexpected serious adverse reactions.***

*Article 37*

*Reporting of adverse events and serious adverse events by the investigator to the sponsor*

1. The investigator shall ***record and document*** ~~***report to the sponsor***~~ adverse events or laboratory abnormalities identified in the protocol as critical to the safety evaluation ***and report them to the sponsor*** in accordance with the reporting requirements and within the time periods specified in the protocol.

2. ***The investigator shall record and document all adverse events unless the protocol provides differently. He shall report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial unless the protocol provides differently.***

The investigator shall ~~***immediately***~~ report serious adverse events to the sponsor ***without undue delay but not later than within 24 hours of obtaining knowledge of the events,*** unless***, for certain serious adverse events,*** the protocol provides~~***, for certain adverse events,***~~ that no ***immediate*** reporting is required. ~~***The investigator shall record all serious adverse events.***~~ Where ~~***necessary***~~ ***relevant***, the investigator shall send a follow-up report to the sponsor ***to allow the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial.***

3. The sponsor shall keep detailed records of all adverse events reported to it by the investigator.

***4. If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial in a subject treated by him or her, the investigator shall, without undue delay, report the serious adverse event to the sponsor.***

*Article 38*

*Reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency*

1. The sponsor ***of a clinical trial performed in at least one Member State*** shall report electronically and without delay to the electronic database referred to in Article 36 all relevant information about suspected unexpected serious adverse reactions to investigational medicinal products insofar as the suspected unexpected serious adverse reaction occurred in a clinical trial conducted by the sponsor, or occurred in a clinical trial related to the sponsor. ***The suspected unexpected serious adverse reactions which shall be reported are as follows:***

***(a) all suspected unexpected serious adverse reactions occurring in the clinical trial, irrespective of whether the suspected unexpected serious adverse reaction has occurred at a trial site in a Member State or in a third country concerned;***

***(b) all suspected unexpected serious adverse reactions related to the same active substance (regardless of pharmaceutical form and strength or indication investigated) in a clinical trial performed exclusively in a third country, if that clinical trial is:***

***(i) sponsored by the same sponsor, or***

***(ii) sponsored by another sponsor who is either part of the same mother company or who develops a medicinal product jointly, on the basis of a formal agreement, with that other sponsor. Provision of the investigational medicinal product or information to a future potential marketing authorisation holder on safety matters should not be considered a joint development.***

***(c) all suspected unexpected serious adverse reactions which are identified by or come to the attention of the sponsor after the end of the clinical trial.***

2. The time period for reporting ***of suspected unexpected serious adverse reactions by the sponsor to the Agency*** shall take account of the ~~***severity***~~ ***seriousness*** of the reaction ***and shall be as follows:***

   ***(a) in the case of fatal and life-threatening suspected unexpected serious adverse reactions, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction;***

   ***(b) in the case of non-fatal and non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction;***

   ***(c) in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or non-life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening.***

   Where necessary to ensure timely reporting, the sponsor may, ***in accordance with section 2.4 of Annex III,*** submit an initial incomplete report followed up by a complete report.

3. Where a sponsor, due to a lack of resources, does not have the possibility to report to the electronic database referred to in Article 36 ***and the sponsor has the agreement of the Member State concerned***, it may report to the Member State where the suspected unexpected serious adverse reaction occurred. That Member State shall report the suspected unexpected serious adverse reaction in accordance with paragraph 1.

*Article 39*

*Annual reporting by the sponsor to the Agency*

1. Regarding ~~***non-authorised***~~ investigational medicinal products other than placebo, ~~***and authorised investigational medicinal products which, according to the protocol, are not used in accordance with the terms of the marketing authorisation***~~, the sponsor shall submit annually by electronic means to the Agency a report on the safety of each investigational medicinal product used in a clinical trial for which it is the sponsor.

***1a. In the case of a clinical trial involving the use of more than one investigational medicinal product, the sponsor may, if provided for in the protocol, submit a single safety report on all investigational medicinal products used in the trial.***

***1b. The annual report referred to in paragraph 1 shall only contain aggregate and anonymised data.***

2. The obligation referred to in paragraph 1 starts with the first authorisation of a clinical trial in accordance with this Regulation. It ends with the end of the last clinical trial conducted by the sponsor with the investigational medicinal product.

*Article 40*

*Assessment by Member States*

1. The Agency shall, by electronic means, forward to the ***~~relevant~~*** Member States ***concerned*** the information reported in accordance with Article 38 and 39.

2. Member States shall cooperate in assessing the information reported in accordance with Articles 38 and 39. ***The Commission may adopt implementing acts in accordance with the procedure laid down in Article 84 to set up or modify the rules on such cooperation.***

***2a. The responsible Ethics Committee shall be involved in the assessment of the information referred to in paragraphs 1 and 2 if it is foreseen by national law.***

***~~Article 41~~***

***~~Annual reporting by the sponsor to the marketing authorisation holder~~***

***~~1. Regarding authorised medicinal products which, according to the protocol, are used in accordance with the terms of the marketing authorisation, the sponsor shall inform annually the marketing authorisation holder of all suspected serious adverse reactions.~~***

***~~2. The obligation referred to in paragraph 1 starts with the first authorisation of a clinical trial in accordance with this Regulation. It ends with the end of the clinical trial.~~***

*Article 42*

*Technical aspects*

Technical aspects for safety reporting in accordance with Articles 37 to 41 are contained in Annex III. ~~***The***~~ ***Where necessary in order to improve the level of protection of subjects, the*** Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to amend Annex III for any of the following purposes:

– ~~***ensuring a high level of protection of subjects;***~~

– improving the information on the safety of medicinal products;

– adapting technical requirements to technical progress;

– ~~***setting up or modifying detailed rules on cooperation on the assessment of the information reported in accordance with Articles 38 and 39;***~~

– taking account of ~~***global***~~ ***international*** regulatory developments in the field of ***safety requirements in*** clinical trials***, endorsed by bodies in which the Union or its Member States participate***.

*Article 43*

*Reporting with regard to auxiliary medicinal products*

Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Chapter 3 of ***Title IX of*** Directive 2001/83/EC.

## Chapter VIII

## Conduct of the trial, supervision by the sponsor, training and experience, auxiliary medicinal products

*Article 44*

*Compliance with the protocol and good clinical practice*

***The sponsor of a clinical trial and the investigator shall ensure that the ~~A~~*** clinical trial ***~~shall be~~ is*** conducted in accordance with the protocol ***and with the principles of good clinical practice***.`

Without prejudice to ***any other provision of Union law or Commission guidelines, ~~Union legislation and specific guidelines of the Commission~~*** the sponsor and the investigator, when drawing up the protocol and when applying this Regulation and the protocol, shall ***also*** take ***appropriate ~~due~~*** account of the quality standards ***and ~~set by the detailed international~~*** guidelines ***~~on good clinical practice~~*** of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The Commission shall make the detailed international guidelines on good clinical practice referred to in the second paragraph publicly available.

*Article 45*

*Monitoring*

***In order to verify that the rights, safety and wellbeing of subjects are protected, that the reported data are reliable and robust, and that the conduct of the clinical trial is in compliance with the requirements of this Regulation t~~T~~***he sponsor shall adequately monitor the conduct of a clinical trial. The extent and nature of the monitoring shall be determined by the sponsor on the basis of ***an assessment that takes into consideration*** all characteristics of the clinical trial, including the following characteristics:

(a) whether the clinical trial is a low-intervention clinical trial;

(b) the objective and methodology of the clinical trial;

(c) the degree of deviation of the intervention from normal clinical practice.

*Article 46*

*Suitability of individuals involved in conducting the clinical trial*

The investigator shall be a medical doctor as defined in national law, or a person following a profession which is recognised in the Member State concerned as qualifying for an investigator because of the necessary scientific knowledge and experience in patient care.

Other individuals involved in conducting a clinical trial shall be suitably qualified by education, training and experience to perform their tasks

*Article 47*

*Suitability of trial sites*

The facilities where the clinical trial is to be conducted shall be suitable for the ***conduct of the*** clinical trial ***in compliance with the requirements of this Regulation***.

*Article 48*

*Tracking, storing,* ***return and*** *destruction* ~~***and return***~~ *of medicinal products*

1. Investigational medicinal products shall be traceable~~.~~ ***. They shall be*** stored, ***returned and/or*** destroyed ~~***and returned***~~ as appropriate and proportionate to ensure subject safety and the reliability and robustness of the data generated in the clinical trial, ***in particular,*** taking into account whether the investigational medicinal product is authorised, and whether the clinical trial is a low-intervention clinical trial.

   The first subparagraph shall also apply to unauthorised auxiliary medicinal products.

2. The relevant information regarding the traceability, storage, ***return and*** destruction ~~***and return***~~ of medicinal products referred to in paragraph 1 shall be contained in the application dossier.

*Article 49*

*Reporting of serious breaches*

1. ***The*** ~~***Where the***~~ sponsor ~~***is aware, with respect to a clinical trial for which it is a sponsor,***~~ ***shall notify the Member States concerned about*** ~~***of***~~ a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach~~***, it shall notify the Member States concerned,***~~ through the EU portal~~***, of that breach*** ***without undue delay but not later than*** within seven days of becoming aware of that breach.

2. For the purposes of this Article, a 'serious breach' means a breach likely to affect to a significant degree the safety and rights of the subjects or the reliability and robustness of the data generated in the clinical trial.

*Article 50*

*Other reporting obligations relevant for subject safety*

1. The sponsor shall notify the Member States concerned through the EU portal ~~***and without undue delay,***~~ of all unexpected events which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 38. ***That notification shall be made without undue delay but no later than in 15 days from the date the sponsor became aware of this event.***

2. The sponsor shall submit to the Member States concerned, through the EU portal, all inspection reports of third country authorities concerning a clinical trial conducted by that sponsor. ***When requested by a Member State concerned, the sponsor shall submit a translation of the report or of its summary in an official language of the Union indicated in the request.***

*Article 51*

*Urgent safety measures*

1. Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects.

2. The sponsor shall ***~~without delay~~ ~~inform~~ notify*** the Member States concerned, through the EU portal, of the event and the measures taken.
***That notification shall be made without undue delay but no later than in 7 days from the date of the measures have been taken.***

3. This Article is without prejudice to Chapters ***~~II~~ III*** and VII.

*Article 52*

*Investigator's brochure*

1. The sponsor shall provide the investigator with the investigator's brochure.

***~~2. The investigator's brochure shall contain all clinical and non-clinical data on the investigational medicinal products relevant to the clinical trial.~~***

3. The investigator's brochure shall be updated where new ***and relevant*** safety information becomes available, and ***shall be reviewed by the sponsor*** at least once per year.

*Article 53*

*Recording, processing, handling and storage of information*

1. All clinical trial information shall be recorded, processed, handled, and stored ***by the sponsor or investigator, as applicable,*** in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable legislation on personal data protection.

2. Appropriate technical and organisational measures shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves the transmission over a network.

*Article 54*

*Clinical trial master file*

The sponsor and the investigator shall keep a clinical trial master file. ***The clinical trial master file shall at all time contain the essential documents relating to that trial which allow verification of the conduct of a clinical trial and the quality of the data generated taking account of all characteristics of the clinical trial, including in particular whether the clinical trial is a low-intervention clinical trial. It shall be readily available, and directly accessible upon request, to the Member States.***

~~***The content of the clinical trial master file shall allow verification of the conduct of a clinical trial, taking account of all characteristics of the clinical trial, including whether the clinical trial is a low-intervention clinical trial.***~~

The clinical trial master file kept by the investigator and that kept by the sponsor may have a different content if this is justified by the different nature of the responsibilities of the investigator and the sponsor.

*Article 55*

*Archiving of the clinical trial master file*

Unless other Union legislation requires archiving for a longer period, the sponsor and the investigator shall archive the content of the clinical trial master file for at least ***25*** ~~***five***~~ years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national legislation.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available ***and accessible***, upon request, to the competent authorities.

Any transfer of ownership of the content of the clinical trial master file shall be documented.
The new owner shall assume the responsibilities set out in this Article.
The sponsor shall appoint individuals within its organisation to be responsible for archives.
Access to archives shall be restricted to those individuals.

The media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible throughout the time period referred to in the first paragraph.

Any alteration to the content of the clinical trial master file shall be traceable.

*Article 56*

*Auxiliary medicinal products*

1. Only authorised auxiliary medicinal products may be used in a clinical trial.

2. Paragraph 1 shall not apply where no authorised auxiliary medicinal product is available in the Union or where the sponsor cannot reasonably be expected to use an authorised auxiliary medicinal product. A justification to this effect shall be included in the protocol.

***3. Member States shall ensure that not authorised auxiliary medicinal products may enter their territories for the purpose of the use in a clinical trial.***

## Chapter IX

## Manufacturing and import of investigational medicinal products and auxiliary medicinal products

*Article 57*

*Scope*

Notwithstanding Article 1, this Chapter shall apply to the manufacture and import of investigational medicinal products and auxiliary medicinal products.

*Article 58*

***Authorisation of ~~M~~m****anufacturing and import****ation*** ***~~authorisation~~***

1. The manufacturing and import of investigational medicinal products in the Union shall be subject to the holding of an authorisation.

2. In order to obtain the authorisation referred to in paragraph 1, the applicant shall meet the following requirements:

   (a) it shall have at its disposal, for manufacture or import, suitable and sufficient premises, technical equipment and control facilities complying with the requirements set out in this Regulation;

   (b) it shall have permanently and continuously at its disposal the services of a***t least one qualified*** person who fulfils the conditions set out in Article 49 (2) and (3) of Directive 2001/83/EC (hereinafter 'qualified person').

3. The applicant shall specify, in the ***application*** ***~~request~~*** for authorisation, the types and pharmaceutical forms of the investigational medicinal product manufactured or imported, the manufacturing or import operations, the manufacturing process where relevant, the site where the investigational medicinal products are to be manufactured ***or the site in the Union to which they are to be imported***, and detailed information concerning the qualified person.

4. Articles 42 to 46 ***point*** (e) of Directive 2001/83/EC shall apply to the ***~~manufacturing and importation~~*** authorisation referred to in paragraph 1.

5. Paragraph 1 shall not apply to any of the following processes:

   (a) re-labelling, ***or*** re-packaging ***~~or reconstitution prior to use or packaging~~***, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State ***concerned*** to carry out such processes, and if the investigational medicinal products are intended to be used exclusively ***in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State*** ***~~by those institutions~~***;

(b) ***preparation ~~the manufacture or import~~*** of radiopharmaceuticals used as diagnostic investigational medicinal products where ***~~those~~ this*** process***~~es~~ ~~are~~ is*** carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process~~es~~, and if the investigational medicinal products are intended to be used exclusively in ***~~those institutions~~ hospitals, health centres or clinics taking part in the same clinical trial in the same Member State***;

(c) the preparation of medicinal products referred to in Article 3(1) and (2) of Directive 2001/83/EC ***for use as investigational medicinal products, where those preparations are carried out in hospitals, health centres or clinics legally authorised in the Member State concerned to carry out such processes and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State***.

6. Member States shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial. They shall subject the processes to regular inspections.

*Article 59*

*Responsibilities of the qualified person*

1. The qualified person shall ensure that each batch of investigational medicinal products manufactured in or imported into the Union complies with the requirements set out in Article 60 and shall certify that those requirements are fulfilled.

2. The certification referred to in paragraph 1 shall be made available by the sponsor at the request of the Member State concerned.

*Article 60*

*Manufacturing and import*

1. Investigational medicinal products shall be manufactured ***~~in~~ by*** applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard subject safety and the reliability and robustness of clinical data generated in the clinical trial (hereinafter 'good manufacturing practice'). The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to specify the ***principles and guidelines*** ***~~detailed requirements~~*** of good manufacturing practice ***and the modalities for inspection*** for ensuring the quality of investigational medicinal products, taking account of subject safety or data reliability and robustness, technical progress and global regulatory developments.

***In addition, the Commission shall also adopt and publish detailed guidelines in line with those principles of good manufacturing practice and revise them when necessary in order to take account of technical and scientific progress.***

2. Paragraph 1 shall not apply to the processes referred to in Article 58(5).

3. Investigational medicinal products imported into the Union shall be manufactured by applying quality standards at least equivalent to those laid down on the basis of this Regulation.

***3a. The Member States shall ensure compliance with the requirements of this Article by means of inspections.***

*Article 61*

*Modification of authorised investigational medicinal products*

Articles 58, 59 and 60 shall apply to authorised investigational medicinal products only as regards any modification of such products not covered by a marketing authorisation

*Article 62*

*Manufacturing of auxiliary medicinal products*

Where the auxiliary medicinal product is not authorised, and where an authorised auxiliary medicinal product is modified while this modification is not covered by a marketing authorisation, it shall be manufactured ***according to good manufacturing practice referred to in Article 60(1) or at least an equivalent standard*** ~~***by applying the necessary standards***~~ to ensure appropriate quality.

## Chapter X
## Labelling

*Article 63*

*Unauthorised investigational and unauthorised auxiliary medicinal products*

1. The following information shall appear on the outer packaging and on the immediate packaging of unauthorised investigational medicinal products and unauthorised auxiliary medicinal products:
   (a) Information to identify contact persons or persons involved in the clinical trial;
   (b) Information to identify the clinical trial;
   (c) Information to identify the medicinal product;
   (d) Information related to the use of the medicinal product.

2. The information ~~***to***~~ ***which shall*** appear on the outer packaging and immediate packaging shall ensure subject safety and reliability and robustness of the data generated in the clinical trial, while taking account of the design of the trial, whether the products are investigational or auxiliary medicinal product, and whether they are products with particular characteristics.

   ***The information which shall appear on the outer packaging and immediate packaging shall be clearly legible.***

   A list of information appearing on the outer packaging and immediate packaging is set out in Annex IV.

*Article 64*

*Authorised investigational and authorised auxiliary medicinal products*

1. Authorised investigational medicinal products and authorised auxiliary medicinal products shall be labelled
   (a) in accordance with Article 63(1); or
   (b) in accordance with Title V of Directive 2001/83/EC.

2. Notwithstanding paragraph 1(b), where the specific circumstances***, provided in the protocol,*** of a clinical trial so require in order to ensure subject safety or the reliability and robustness of data generated in a clinical trial, additional particulars relating to the identification of the trial and of the contact person shall appear on the outer packaging and the immediate packaging of authorised investigational medicinal products. A list of these additional particulars appearing on the outer packaging and immediate packaging is set out in Annex IV.

*Article 65*

*Radiopharmaceutical**s** used as investigational medicinal product**s or as auxiliary medicinal products** for a medical diagnosis*

Articles 63 and 64 shall not apply to radiopharmaceuticals used as ***diagnostic*** investigational medicinal product***s or as diagnostic auxiliary medicinal products*** ~~***for a medical diagnosis***~~.

The products referred to in the first paragraph shall be labelled appropriately in order to ensure subject safety and the reliability and robustness of data generated in the clinical trial.

*Article 66*

*Language*

The language of the information on the label shall be determined by the Member State concerned. The medicinal product may be labelled in several languages.

*Article 67*

*Delegated act*

The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to amend Annex IV to ensure subject safety and the reliability and robustness of data generated in a clinical trial or to take account of technical progress.

## Chapter XI
## Sponsor and investigator

*Article 68*

*Sponsor*

A clinical trial may have one or several sponsors.

Any sponsor may delegate***, in a written contract,*** any or all of its tasks to an individual, a company, an institution or an organisation. Such delegation shall be without prejudice to the responsibility of the sponsor***, in particular regarding subject safety and the reliability and robustness of the data generated in the clinical trial***.

The investigator and the sponsor may be the same person.

*Article 69*

*Co-sponsorship*

1. ~~*Where*~~ ***Without prejudice to Article 70, where*** a clinical trial has more than one sponsor, all sponsors shall be subject to the responsibilities of a sponsor under this Regulation, unless the sponsors decide otherwise in a ***written*** contract setting out their respective responsibilities. Where the contract does not specify to which sponsor a given responsibility is attributed, that responsibility shall lie with all sponsors.

2. By way of derogation from paragraph 1, all sponsors shall be responsible for establishing one sponsor responsible for each of the following:

(a) compliance with the obligations of a sponsor in the authorisation procedures set out in Chapters II and III;

(b) ***to be a contact point for receiving*** ~~***providing responses to***~~ all questions from subjects, investigators or any Member State concerned regarding the clinical trial ***and providing responses to them***;

(c) implementing measures taken in accordance with Article 74.

***Article 69a***

***Principal investigator***

***A principal investigator shall ensure compliance of a clinical trial at a clinical trial site with the requirements of this Regulation.***

***The principal investigator shall assign tasks among the members of the team of investigators in a way which is not compromising subject safety and the reliability and robustness of the data generated in the clinical trial at that clinical trial site.***

*Article 70*

~~***Contact person***~~ ***Legal representative*** *of the sponsor in the Union*

***1.*** Where the sponsor of a clinical trial is not established in the Union, that sponsor shall ensure that a ***natural or legal*** ~~***contact***~~ person is established in the Union ***as its legal representative***. ~~***That contact person***~~ ***The legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to this Regulation, and*** shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication to that ~~***contact person***~~ ***legal representative*** shall be considered as communication to the sponsor.

***2. Member States may choose not to apply paragraph 1 of this Article as regards clinical trials to be conducted solely on their territory, or on their territory and the territory of third countries, provided that they ensure that the sponsor establishes at least a contact person on their territory in respect of that clinical trial who shall be the addressee for all communications with the sponsor provided for in this Regulation.***

***3. As regards clinical trials to be conducted in more than one Member State, all those Member States may choose not to apply paragraph 1 provided that they ensure that the sponsor establishes at least a contact person in the Union in respect of that clinical trial who shall be the addressee for all communications with the sponsor provided for in this Regulation.***

*Article 71*

*Liability*

This Chapter shall not affect the civil and criminal liability of the sponsor, investigator, or persons to whom the sponsor has delegated tasks.

## Chapter XII

## Damage compensation~~, *insurance and national indemnification mechanism*~~

*Article 72*

*Damage compensation*

~~***For clinical trials other than low-intervention clinical trials, the sponsor shall ensure that compensation in accordance with the applicable laws on liability of the sponsor and the investigator is provided for any damage suffered by the subject. This damage compensation shall be provided independently of the financial capacity of the sponsor and the investigator.***~~

***1. Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted on their territory are in place in the form of insurance or a guarantee or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk.***

***2. The sponsor and the investigator shall make use of the system referred to in paragraph 1 in the form appropriate for the Member State concerned where the clinical trial is conducted.***

*3. Member States shall not require any additional use of the system referred to in paragraph 1 from the sponsor for low-intervention clinical trials if any possible damage that could be suffered by a subject resulting from the use of the investigational medicinal product in accordance with the protocol of that specific clinical trial on the territory of that Member State is covered by the applicable compensation system already in place.*

~~*Article 73*~~

~~*National indemnification mechanism*~~

~~*1. Member States shall provide for a national indemnification mechanism for compensating damage as referred to in Article 72.*~~

~~*2. The sponsor shall be deemed to comply with Article 72 where it makes use of the national indemnification mechanism in the Member State concerned.*~~

~~*3. The use of the national indemnification mechanism shall be free of charge where, for objective reasons, the clinical trial was not intended, at the time of submission of the application for authorisation of that clinical trial, to be used for obtaining a marketing authorisation for a medicinal product.*~~

~~*For all other clinical trials, the use of the national indemnification mechanism may be subject to a fee. Member States shall establish that fee on a not-for-profit basis, taking into account the risk of the clinical trial, the potential damage, and the likelihood of the damage.*~~

## Chapter XIII

## Supervision by Member States, Union inspections and controls

*Article 74*

*Corrective measures to be taken by Member States*

1. Where a Member State concerned has ***justified*** ~~***objective***~~ grounds for considering that the requirements set out in this Regulation are no longer met, it may take the following measures ***on its territory***:

   (a) ~~***it may terminate early***~~ ***revoke the authorisation of a*** ~~***the***~~ clinical trial;

   (b) ~~***it may***~~ ***suspend*** ~~***the***~~ ***a*** clinical trial;

   (c) ~~***it may***~~ ***require the sponsor to*** modify any aspect of the clinical trial.

***1a. Before the Member State concerned takes the measure referred to in paragraph 1 it shall, except where immediate action is required, ask the sponsor and/or the investigator for their opinion, to be delivered within one week.***

2. ***The Member State concerned shall immediately after taking the*** ~~***The***~~ measures referred to in paragraph 1 ~~***shall be communicated to***~~ ***inform*** all Member States concerned through the EU portal.

***3. Each Member State concerned may consult the other Member States concerned before taking the measures referred to in paragraph 1.***

*Article 75*

*Member State inspections*

1. Member States shall appoint inspectors to supervise compliance with this Regulation. They shall ensure that those inspectors are adequately qualified and trained.

2. Inspections shall be conducted under the responsibility of the Member State where the inspection takes place.

3. Where a Member State concerned intends to carry out an inspection ***on its territory or in a third country*** with regard to one or several clinical trials which are conducted in more than one Member State concerned, it shall notify its intention to the other Member States concerned, the Commission and the Agency, through the EU portal, and shall inform them of its findings after the inspection.

***3a. Inspections fees, if any, may be waived for non-commercial sponsors.***

4. ~~***The***~~ ***In order to efficiently use the resources available and to avoid duplications, the*** Agency shall coordinate ***the*** cooperation ***between Member States concerned*** on inspections ~~***between Member States, inspections***~~ conducted ~~***by***~~ ***in*** Member States**,** in third countries, and inspections conducted in the framework of a marketing authorisation application under Regulation (EC) No 726/2004.

5. Following an inspection, the Member State under whose responsibility the inspection has been conducted shall draw up an inspection report. That Member State shall make the inspection report available to the ***inspected entity and the*** sponsor of the relevant clinical trial and shall submit the inspection report through the EU portal to the EU database.

~~***When making the inspection report available to the sponsor, the Member State referred to in the first subparagraph shall ensure that confidentiality is protected.***~~

6. The Commission shall specify the modalities for the inspection procedures ***including the qualification and training of inspectors*** by the way of implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 84(2).

*Article 76*

*Union controls ~~and Union inspections~~*

1. The Commission may conduct controls in order to verify
   (a) whether Member States correctly supervise compliance with this Regulation;
   (b) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that point 8 of Annex I to Directive 2001/83/EC is complied with;
   (c) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that Article 25(***~~3~~5***) of this Regulation is complied with.

***1a. The Union controls mentioned in paragraph 1, point (a) shall be organised in cooperation with the concerned Member States.***

***The Commission in cooperation with Member States shall prepare a programme for the types of controls referred to in points (b) and (c) of paragraph 1.***

***The Commission shall report on the findings of each Union control carried out. These reports shall, if appropriate, contain recommendations. The Commission shall submit these reports through the EU portal to the EU database.***

***~~2. The Commission may conduct inspections where it considers necessary.~~***

## Chapter XIV
## IT Infrastructure

*Article 77*

*EU portal*

The ~~***Commission***~~ ***European Medicines Agency*** shall***, in collaboration with the Member States and the Commission,*** set up and maintain a portal at Union level as a single entry point for the submission of data and information relating to clinical trials in accordance with this Regulation. ***The portal shall be technically advanced and user-friendly so as to avoid unnecessary work.***

Data and information submitted through the EU portal shall be stored in the EU database referred to in Article 78.

*Article 78*

*EU database*

1. The ~~***Commission***~~ ***Agency*** shall***, in collaboration with the Member States and the Commission,*** set up and maintain a database at Union level (hereinafter, the 'EU database'). The ~~***Commission***~~ ***Agency*** shall be considered controller of the database ***and shall be responsible for avoiding unnecessary duplication between that database and the EudraCT and EudraVigilance databases***.

   The EU database shall contain the data and information submitted in accordance with this Regulation.

   ***This database shall identify each clinical trial by a unique EU trial number. The sponsor shall refer to this EU trial number in any subsequent clinical trial application.***

2. The EU database shall be established to enable the co-operation between the competent authorities of the Member States to the extent that it is necessary for the application of this Regulation and to search for specific clinical trials. It shall also ***facilitate the communication between sponsors and Member States concerned and*** enable sponsors to refer to previous submissions of an application for authorisation of a clinical trial or a substantial modification. ***It shall also enable citizens of the Union to have access to clinical information about medicinal products. To this end all data held in the database shall be in an easily searchable format, all related data shall be grouped together by way of the EU trial number, and hyperlinks shall be provided to link together related data and documents held on the EU database and other databases managed by the Agency.***

***2a. The EU database shall support the recording and submission to the EU dictionary of medicinal products and substances, established by Article 57 of Regulation (EC) No 726/2004, of all the information on medicinal products/substances without a marketing authorisation in the Union that is necessary for the maintenance of that dictionary. To this effect and also with the purpose of enabling the sponsor to cross-refer to prior applications, an EU medicinal product number (EU MP number) should be issued for every medicinal product without a marketing authorisation and an EU active substances code should be issued for each new active substance not previously authorised as part of a medicinal product in the EU. This should be done before or during the application for authorisation of the first clinical trial with that product or active substance submitted according to this Regulation. Those numbers should be mentioned in all subsequent clinical trials applications and modifications.***

***The data submitted describing the medicinal product and substances shall comply with EU and international standards for the identification of medicinal products and active substances. When the investigational medicinal product already has a marketing authorisation in the EU and/or the active substance is part of a medicinal product with a marketing authorisation in the EU, the relevant product and active substance numbers shall be referred to in the clinical trial application.***

3. The EU database shall be publicly accessible unless, for all or parts of the data and information contained therein, confidentiality is justified on any of the following grounds:
   – protecting personal data in accordance with Regulation (EC) No 45/2001;
   – protecting commercially confidential information***, in particular through taking into account the status of the marketing authorisation for the medicinal product unless there is an overriding public interest in disclosure***;
   – ***protecting confidential communication between Member States in relation to the preparation of the assessment report;***
   – ensuring effective supervision of the conduct of a clinical trial by Member States.

***3a. Without prejudice to paragraph 3, unless there is an overriding public interest in disclosure, data in the application dossier shall not be publicly accessible before the decision on the clinical trial has been made.***

4. The EU database shall contain personal data only insofar as this is necessary for the purposes of paragraph 2.

5. No personal data of subjects shall be publicly accessible.

***5a. The user interface of the EU database shall be available in all Union official languages.***

6. The sponsor shall permanently update in the EU database information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial by the Member States.

7. ***The Agency, T****~~t~~*he Commission and Member States shall ensure that the data subject may effectively exercise his or her rights to information, to access, to rectify and to object in accordance with Regulation (EC) No 45/2001 and national data protection legislation implementing Directive 95/46/EC respectively. They shall ensure that the data subject may effectively exercise the right of access to data relating to him or her, and the right to have inaccurate or incomplete data corrected and erased. Within their respective responsibilities, ***the Agency, the*** Commission and Member States shall ensure that inaccurate and unlawfully processed data is deleted, in accordance with the applicable legislation. Corrections and deletions shall be carried out as soon as possible, but no later than within 60 days after a request is made by a data subject.

***Article 78a***

***Functionality of the EU portal and the EU database***

***1. The Agency shall, in collaboration with the Member States and the Commission draw up the functional specifications for the EU portal and the EU database, together with the timeframe for their implementation.***

***2. The Management Board of the Agency shall on the basis of an independent audit report inform the Commission when it has verified that the EU portal and the EU database have achieved full functionality and the systems meet the functional specifications drawn up pursuant to paragraph 1.***

***3. The Commission shall, when it is satisfied that the conditions referred to in paragraph 2 have been fulfilled, publish a notice to that effect in the Official Journal of the European Union.***

## Chapter XV

## Cooperation between Member States

*Article 79*

*National contact points*

1. Each Member State shall designate one national contact point in order to facilitate the functioning of the procedures set out in Chapters II and III.

2. Each Member State shall communicate the contact point to the Commission. The Commission shall publish a list of the contact points.

*Article 80*

*Support by the **Agency and the** Commission*

The ***Agency*** ~~***Commission***~~ shall support the functioning of the cooperation of the Member States in the framework of the authorisation procedures referred to in Chapters II and III of this Regulation ***by maintaining and updating the EU portal and EU database referred to in Articles 77 and 78 in accordance with the experience acquired during the implementation of this Regulation***.

***The Commission shall support*** ~~***and***~~ the functioning of the cooperation ***of the Member States*** referred to in Article 40(2).

*Article 81*

*Clinical Trials Coordination and Advisory Group*

1. A Clinical Trials Coordination and Advisory Group (CTAG), composed of the national contact points referred to in Article 79 is hereby established.

2. The CTAG shall have the following tasks:
   (a) support the exchange of information between the Member States and the Commission on the experience acquired with regard to the implementation of this Regulation;

(b) assist the Commission in providing for the support referred to in Article 80;

***(ba) prepare recommendations on criteria regarding the selection of a reporting Member State.***

3. The CTAG shall be chaired by a representative of the Commission.

4. The CTAG shall meet at regular intervals and whenever the situation requires, on a request from the Commission or a Member State. ***Any item of the agenda of the meeting shall be placed at the request of the Commission or a Member State.***

5. The secretariat shall be provided by the Commission.

***5a. The CTAG shall draw up its rules of procedure. The rules of procedure shall be made public.***

## Chapter XVI

## Fees

*Article 82*

*General principle*

This Regulation shall be without prejudice to the possibility for Member States to levy a fee for the activities set out in this Regulation, provided that the level of the fee is set in a transparent manner and on the basis of cost recovery principles. ***Member States may establish reduced fees for non-commercial clinical trials.***

*Article 83*

*One fee per activity per Member State*

A Member State shall not require, for an assessment as referred to in Chapters II and III, multiple payments to different bodies involved in this assessment.

## Chapter XVII

## Implementing acts and Delegated acts

*Article 84*

*Committee*

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use established by Directive 2001/83/EC. That committee shall be a committee within the meaning of Regulation (EU) No 182/2011.

2. Where reference is made to this paragraph, Article 5 of Regulation (EU) No 182/2011 shall apply.

~~***Where the opinion of the committee is to be obtained by written procedure, that procedure shall be terminated without result when, within the time-limit for delivery of the opinion, the chair of the committee so decided or a simple majority of committee members so request.***~~

***Where the committee delivers no opinion, the Commission shall not adopt the draft implementing act and the third subparagraph of Article 5(4) of Regulation (EU) No 182/2011 shall apply.***

*Article 85*

*Exercise of the delegation*

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.

2. The delegation of power referred to in Articles 27, ***35a,*** 42, 60 and 67 shall be conferred on the Commission for ***a period of five years*** ~~***an indeterminate period of time***~~ from ***the date referred to in the second paragraph of Article 93*** ~~***[the date of entry into force of this Regulation]***~~***. The Commission shall draw up a report in respect of the delegated powers not later than 6 months before the end of the five year period. The delegation of powers shall be automatically extended for periods of an identical duration, unless the European Parliament or the Council revokes it in accordance with Paragraph 3.***

3. The delegation of power referred to in Articles 27, ***35a,*** 42, 60 and 67 may be revoked at any time by the European Parliament or by the Council. A decision of revocation shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the Official Journal of the European Union or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.

4. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

5. A delegated act adopted pursuant to Articles 27, ***35a,*** 42, 60 and 67 shall enter into force only if no objection has been expressed either by the European Parliament or the Council within a period of 2 months of notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by 2 months at the initiative of the European Parliament or the Council.

## Chapter XVIII
## Miscellaneous provisions

*Article 86*

***Specific requirements for special groups of m~~M~~****edicinal products* ***~~containing, consisting of or derived from cells~~***

This Regulation shall not affect the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from those cells, ***or medicinal products used as abortifacients, or medicinal products containing narcotic substances within the meaning of the international conventions in force such as the United Nations Convention of 1961~~on grounds not dealt with in this Regulation~~***. The Member States shall communicate the national legislation concerned to the Commission.

***No gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity.***

*Article 87*

*Relation with other legislation*

This Regulation shall be without prejudice to, Council Directive 97/43/Euratom[12], Council Directive 96/29/Euratom[13], Directive 2001/18/EC[14] of the European Parliament and of the Council, ***Directive 2004/23/EC***[15] ***of the European Parliament and of the Council, Directive 2002/98/EC***[16] ***of the European Parliament and of the Council, Directive 2010/45/EC***[17] ***of the European Parliament and of the Council,*** and Directive 2009/41/EC[18] of the European Parliament and of the Council.

*Article 88*

*Investigational medicinal products**, other products and procedures** free of charge for the subject*

Without prejudice to the Member States' competence for the definition of their health policy and for the organisation and delivery of health services and medical care, the costs for investigational medicinal products***, auxiliary medicinal products, medical devices used for their administration and procedures specifically required by the protocol*** shall not be borne by the subject ***unless national legislation in the Member State concerned provides otherwise***.

*Article 89*

*Data Protection*

1. Member States shall apply Directive 95/46/EC to the processing of personal data carried out in the Member States pursuant to this Regulation.

2. Regulation (EC) No 45/2001 shall apply to the processing of personal data carried out by the Commission and the European Medicines Agency pursuant to this Regulation.

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12 OJ L 180, 9.7.1997, p. 22.
13 OJ L 159, 29.6.1996, p. 1.
14 OJ L 106, 17.4.2001, p. 1.
15 OJ L ….
16 OJ L ….
17 OJ L ….
18 OJ L 125, 21.5.2009, p. 75.

*Article 89a*

***Penalties***

***1. Member States shall lay down rules on penalties applicable to infringements of this Regulation and shall take all measures necessary to ensure that they are implemented. The penalties provided for shall be effective, proportionate and dissuasive.***

***2. The rules referred to in paragraph 1 shall address, inter alia, the following:***

***(a) non-compliance with the provisions laid down in this Regulation on submission of information intended to be made publicly available to the EU database;***

***(b) non-compliance with the provisions laid down in this Regulation on subject safety.***

*Article 90*

*Civil and criminal liability*

This Regulation is without prejudice to national and Union rules on the civil and criminal liability of the sponsor or the investigator.

## Chapter XIX
## Final provisions

*Article 91*

*Repeal*

1. Directive 2001/20/EC is repealed as ***from the date referred to in the second paragraph of Article 93*** ~~***of [please set a specific date - two years after publication of this Regulation]***~~.

2. By way of derogation from ~~the~~ paragraph 1, where the request for authorisation of a clinical trial has been submitted before the date ~~***provided for***~~ ***referred to*** in ***the second paragraph of*** Article ~~***92(2)***~~ ***93*** ~~***[application date]***~~ pursuant to Directive 2001/20/EC, that clinical trial shall continue to be governed by that Directive until ***three years from the date referred to in that paragraph*** ~~***[please set a specific date – five years after publication of this Regulation]***~~.

3. References to Directive 2001/20/EC shall be construed as references to this Regulation and shall be read in accordance with the correlation table laid down in Annex V.

***Article 91a***

***Review***

***Five years after the date referred to in the second paragraph of Article 93, and every five years thereafter, the Commission shall present a report to the European Parliament and the Council, on the application of this Regulation. The report shall include an assessment of the impact that the Regulation has had on scientific and technological progress, comprehensive information on the different types of clinical trials authorised pursuant to this Regulation, and the measures required in order to maintain the competitiveness of European clinical research. The Commission shall, if appropriate, present a legislative proposal based on the report in order to update the provisions set out in this Regulation.***

*Article 92*

*Transitional provision*

By way of derogation from Article 91(1), where the request for authorisation of a clinical trial is submitted between ***six months after the publication concerning the functionality of the EU database and the EU Portal pursuant to Article 78a(3) and 18 months after that publication or, if that publication occurs earlier than*** [*please set a specific date -* ~~*two years*~~ ***18 months*** *from the publication of this Regulation*] ***between [please set a specific date - two years from the publication of this Regulation]*** and [*please set a specific date - three years after publication*] that clinical trial may be started in accordance with Articles 6, 7 and 9 of Directive 2001/20/EC. That clinical trial shall continue to be governed by that Directive until ***42 months after the publication, or if the publication occurs earlier than [please set a specific date - 18 months from the publication of this Regulation] until*** [*please set a specific date – five years after publication of this Regulation*].

*Article 93*

*Entry into force*

This Regulation shall enter into force on the twentieth day following that of its publication in the Official Journal of the European Union.

It shall apply as from ***6 months after the publication concerning the functionality of the EU database and the EU Portal pursuant to Article 78a(3) but in any event no earlier than*** [*please set a specific date - two years after* ~~***its***~~ ***the*** *publication* ***of the Regulation***].

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels,

| | |
|---|---|
| *For the European Parliament* | *For the Council* |
| *The President* | *The President* |

# ANNEX I

## Application dossier for initial application

### ~~1~~*A*. INTRODUCTION AND GENERAL PRINCIPLES

1. The sponsor shall, where appropriate, refer to ***any*** previous applications. If these applications have been submitted by another sponsor, ~~a~~ ***the*** written agreement from that sponsor shall be submitted.

***1a. Where a clinical trial has more than one sponsor, detailed information of the responsibilities of the sponsors shall be submitted in the application dossier.***

2. The application shall be signed by the sponsor ***or a representative of the sponsor***. This signature confirms that the sponsor is satisfied that:
   - the information provided is complete;
   - the attached documents contain an accurate account of the information available;
   - the clinical trial will be conducted in accordance with the protocol***; and***
   - ***the clinical trial will be conducted in accordance with this Regulation***.

3. The application dossier for an application referred to in Article 11 shall be limited to sections 2 to 10 of this Annex.

4. Without prejudice to Article 26, the application dossier for an application referred to in Article 14 shall be limited to sections 11 to 17 of this Annex.

### ~~2~~*B*. COVER LETTER

5. The cover letter shall ***specify the EU trial number and the universal trial number and shall*** draw attention to ***any features which are particular to*** ~~***peculiarities of***~~ the trial.

6. However, in the cover letter it is not necessary to reproduce information already contained in the EU application form, with the following exceptions:
   - specific features of the trial population, such as subjects not able to give informed consent ~~***or***~~ minors***, or pregnant or breastfeeding women***;
   - whether the trial involves the first administration of a new active substance to humans;
   - whether scientific advice relating to the trial or investigational medicinal product has been given by the Agency, ~~***the national competent authority of***~~ a Member State or third country; and
   - whether the trial is part or is intended to be part of a Paediatric Investigation Plan (PIP) as referred to in Title II, Chapter 3, of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use (if the Agency has already issued a decision on the PIP, the cover letter contains the link to the decision of the Agency on its website);
   - whether investigational medicinal products or auxiliary medicinal products are a narcotic***,*** ~~***and***~~ psychotropic ***or radiopharmaceutical***;
   - ***whether the investigational medicinal products consist of or contain a genetically-modified organism or organisms;***
   - whether the sponsor has obtained an orphan designation for the investigational medicinal product ***for an orphan condition*** ~~***or the disease***~~***;***
   - ***a comprehensive list, including the regulatory status of all investigational medicinal products and a list of all auxiliary medicinal products;***
   - ***a list of medical devices which are to be investigated in the clinical trial but which are not part of the investigational medicinal product or products, together with a statement as to whether the medical devices are CE-marked for the intended use***.

7. The cover letter shall indicate where the ~~***relevant***~~ information ***listed in paragraph 6*** is contained in the application dossier.

***7a. The cover letter shall indicate if the trial is considered by the sponsor to be a low-intervention trial and contain a detailed justification thereof.***

***7b. The cover letter shall indicate if the methodology of the clinical trial requires that groups of individual subjects rather than individual subjects are allocated to receive different investigational medicinal products in a clinical trial, and as a consequence informed consent will be obtained by simplified means.***

8. The cover letter shall indicate ~~***where in***~~ ***the location in*** the application dossier ~~***the reference safety information is contained***~~ ***of the information necessary*** for assessing whether an adverse reaction is a suspected unexpected serious adverse reaction ***(i.e. the reference safety information)***.

9. In the case of a resubmission, the cover letter shall ***specify the EU trial number for the previous clinical trial application*** ~~***and***~~ highlight the changes as compared to the previous submission ***and, if applicable, specify how any unresolved issues in the previous submission have been addressed***.

## ~~*3C*~~. EU APPLICATION FORM

10. The EU application form, duly ~~***filled in***~~ ***completed***.

## ~~*4D*~~. PROTOCOL

11. The protocol shall describe the objective, design, methodology, statistical considerations, ***purpose*** and organisation of ~~***a***~~ ***the*** trial.

12. The protocol shall be identified by ***the following:***
    - the title ***of the trial;***~~,~~
    - ***the EU trial number;***
    - the sponsor's protocol code number specific for all versions of it (if ~~***available***~~ ***relevant)***~~,~~***;***
    - the date and number of the version, to be updated when it is amended, ~~***and***~~

- a short title or name assigned to ~~*it*~~ ***the protocol;***
- ***the name and address of the sponsor, as well as the name and function of the representative or representatives of the sponsor authorised to sign the protocol or any substantial modification to the protocol***.

***12a. The protocol shall, when possible, be written in an easily accessible and searchable format, rather than scanned images.***

13. ~~*In particular, t*~~***T***he protocol shall ***at least*** include ***the following***:
    - ~~*a clear and unambiguous definition of the end of the clinical trial in question (in most cases this will be the date of the last visit of the last subject; any exceptions to this are justified in the protocol);*~~
    - ~~*a discussion of the relevance of the clinical trial and its design to allow assessment in accordance with Article 6;*~~
    - ***a statement that the clinical trial shall be conducted in compliance with the protocol, with this Regulation and with the principles of good clinical practice;***
    - ***a comprehensive list of all investigational medicinal products and all auxiliary medicinal products;***
    - ***a summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial;***
    - ***a summary of the known and potential risks and benefits including*** an evaluation of the anticipated benefits and risks to allow assessment in accordance with Article 6***, for emergency trial subjects, the scientific grounds for expecting that their participation has the potential to produce a direct clinically relevant benefit shall be documented***;
    - ***in case patients were involved in the design of the trial, a description of how;***
    - ~~*inclusion and exclusion criteria;*~~
    - ***a description of and justification for the dosage, the dosage regime, the route and mode of administration, and the treatment period for all investigational medicinal products and auxiliary medicinal products;***

- ***a statement of whether the investigational medicinal products and auxiliary medicinal products used in the clinical trial are authorised; if authorised, whether they are to be used in the clinical trial in accordance with the terms of their marketing authorisations, and a justification for the use of non-authorised auxiliary medicinal products in the clinical trial;***
- ~~***a justification for including subjects who are incapable of giving informed consent or other special populations, such as minors;***~~
- ***a description of the groups and sub-groups of the subjects participating in the clinical trial, including, where relevant, groups of subjects with specific needs (ex: age, gender, participation of healthy volunteers, patients with rare and ultra rare diseases);***
- ~~***if elderly persons or women are excluded from the clinical trial, an explanation and justification for these exclusion criteria;***~~
- ~~***a detailed description of the recruitment and informed-consent procedure, especially when subjects are incapable of giving informed consent;***~~
- ~~***a summary of monitoring arrangements;***~~
- ***references to literature and data that are relevant to the trial, and that provide background for the trial;***
- ***a discussion of the relevance of the clinical trial to allow assessment in accordance with Article 6;***
- ***a description of the type of trial to be conducted and a discussion of the trial design (including a schematic diagram of trial design, procedures and stages, if relevant);***
- ***specification of the primary endpoints and the secondary endpoints, if any, to be measured during the clinical trial;***
- ***a description of the measures taken to minimise bias, including ,if applicable, randomisation and blinding;***
- ***a description of the expected duration of subject participation and a description of the sequence and duration of all clinical trial periods, including follow-up, if relevant;***

- ***a clear and unambiguous definition of the end of the clinical trial in question (in most cases this will be the date of the last visit of the last subject; any exceptions to this shall be justified in the protocol);***
- ***a description of the criteria for discontinuing parts of the clinical trial or the entire clinical trial;***
- ***arrangements for the maintenance of clinical trial treatment randomisation codes and procedures for breaking codes, if relevant;***
- ***a description of procedures for the identification of data to be recorded directly on the Case Report Forms (CRFs) considered as source data;***
- ***a description of the arrangements to comply with the applicable rules for the collection, storage and future use of biological samples from trial subjects, where applicable, unless contained in a separate document;***
- ***a description of the arrangements, for tracing, storing, destroying and returning the investigational medicinal product and unauthorised auxiliary medicinal product in accordance with Article 48;***
- ***a description of the statistical methods to be employed, including, if relevant:***
  - ***timing of any planned interim analysis and the number of subjects planned to be enrolled;***
  - ***reasons for choice of sample size;***
  - ***calculations of the power of the trial and clinical relevance;***
  - ***the level of significance to be used;***
  - ***criteria for the termination of the trial;***
  - ***procedures for accounting for missing, unused, and spurious data and for reporting any deviation from the original statistical plan;***
  - ***the selection of subjects to be included in the analyses;***
- ***a description of the subject inclusion and exclusion criteria, including criteria for withdrawing individual subjects from treatment or from the clinical trial;***
- ***a description of procedures relating to the withdrawn of subjects from treatment or from the clinical trial including procedures for the collection of data regarding withdrawn subjects, procedures for replacement of subjects and the follow-up of subjects that have withdrawn from treatment or from the trial;***

- ***a justification for including subjects who are incapable of giving informed consent or other special populations, such as minors;***
- ***if a specific gender or age group is excluded from or underrepresented in the trials, an explanation of the reasons and justification for these exclusion criteria;***
- ***a detailed description of the recruitment and informed-consent procedure, especially when subjects are incapable of giving informed consent;***
- ***a description of the treatments, including medicinal products, which are permitted or not permitted, before or during the trial;***
- ***a description of the accountability procedures for the supply and administration of medicinal products to subjects including the maintenance of blinding, if applicable;***
- ***a description of procedures for monitoring subject compliance, if applicable;***
- a ~~***summary***~~ ***description*** of ~~***monitoring***~~ arrangements ***for monitoring the conduct of the clinical trial***;
- ~~***a description of the publication policy;***~~
- a description of the arrangements for taking care of the subjects after their participation in the trial has ended, where such additional care is necessary because of the subjects' participation in the trial and where it differs from that normally expected for the medical condition in question;
- ~~***a description of the arrangements, if any, for tracing, storing, destroying and returning the investigational medicinal product and auxiliary medicinal product in accordance with Article 48;***~~
- ***a specification of the efficacy and safety parameters as well as the methods and timing for assessing, recording, and analysing of these parameters;***
- ***a description of ethical considerations relating to the clinical trial if those have not been described elsewhere;***
- ***a statement from the sponsor (either in the protocol or in a separate document) confirming that the investigators and institutions involved in the clinical trial shall permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents;***

- ***a specification of the estimated end date of the trial and a justification thereof if it is not the date of the last visit of any subject;***
- ***a description of the publication policy;***
- ***duly substantiated reasons for submission of the summary of the results of the clinical trials after more than one year;***
- a description of the arrangements to comply with the applicable rules on the protection of personal data; in particular organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed;
- a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects concerned in clinical trials;
- a description of measures that will be implemented in case of data security breach in order to mitigate the possible adverse effects;
- ***a justification for the gender and age allocation of trial subjects;***
- ~~***duly substantiated reasons for submission of the summary of the results of the clinical trials after more than one year;***~~
- ~~***a justification for the use of non-authorised auxiliary medicinal products.***~~

14. If a clinical trial is conducted with an active substance available in the European Union under different trade names in a number of authorised medicinal products, the protocol may define the treatment in terms of the active substance or Anatomical Therapeutic Chemical (ATC) code (level ~~3~~ 5) only and not specify the trade name of each product.

15. With regard to the notification of adverse events, the protocol shall identify ***the categories of:***
    - adverse events or laboratory anomalies that are critical to safety evaluations and ~~***are to***~~ ***must*** be reported ***by the investigator*** to the sponsor~~***;***~~, and
    - serious adverse events which do not require ***immediate*** reporting by the investigator ***to the sponsor***.

***15a. The protocol shall describe procedures for:***

- ***eliciting and recording adverse events by the investigator, and the reporting of relevant adverse events by the investigator to the sponsor,***
- ***reporting by the investigator to the sponsor of those serious adverse events which have been identified in the protocol as not requiring immediate reporting;***
- ***reporting of suspected unexpected serious adverse reactions by the sponsor to the EudraVigilance database; and***
- ***follow-up of subjects after adverse reactions including the type and duration of follow-up.***

***15b. In case the sponsor intends to submit a single safety report on all investigational medicinal products used in the trial in accordance with Article 39(1a), the protocol shall indicate the reasons therefor.***

16. Issues regarding labelling and the unblinding of investigational medicinal products shall be addressed in the protocol, where necessary.

***16a. The protocol shall be accompanied by the Charter of the Data Safety Monitoring Committee, if applicable.***

17. The protocol shall be accompanied by a synopsis of the protocol.

***~~5~~E.* INVESTIGATOR'S BROCHURE (IB)**

***17a. An investigator's brochure, which has been prepared in accordance with the state of scientific knowledge and international guidance, shall be submitted.***

18. The purpose of the IB is to provide the investigators and others involved in the trial with information to facilitate their understanding of the rationale for, and their compliance with, key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures.

19. The information in the IB shall be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. It shall be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the investigational medicinal product in the trial and be presented in the form of summaries.

20. If the investigational medicinal product is authorised, and is used according to the terms of the marketing authorisation, the approved summary of product characteristics (SmPC) shall be the IB. If the conditions of use in the clinical trial differ from those authorised, the SmPC shall be supplemented with a summary of relevant non-clinical and clinical data that support the use of the investigational medicinal product in the clinical trial. Where the investigational medicinal product is identified in the protocol only by its active substance, the sponsor shall select one SmPC as equivalent to the IB for all medicinal products that contain that active substance and are used at any clinical trial site.

21. For a multinational trial where the medicinal product to be used in each Member State is the one authorised at national level, and the SmPC varies among Member States, the sponsor shall choose one SmPC for the whole clinical trial. This SmPC shall be the one best suited to ensure patient safety.

22. If the IB is not a SmPC, it shall contain a clearly identifiable section ***called the 'Reference Safety Information' (RSI). In accordance with points 10 and 11 of Annex III, the RSI shall contain product information on the investigational medicinal product and information on how to determine*** ~~***determining***~~ what adverse reactions are to be considered as expected adverse reactions, ***and*** ~~***including information***~~ on the frequency and nature of the***se*** adverse reactions ~~***('reference safety information')***~~.

## ~~*6F.*~~ DOCUMENTATION RELATING TO COMPLIANCE WITH GOOD MANUFACTURING PRACTICE (GMP) FOR THE INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

23. As regards documentation relating to GMP compliance, the following shall apply.

24. ~~*In the following cases, no*~~ ***No*** documentation needs to be submitted ***where the investigational medicinal product is authorised and is not modified, whether or not it is manufactured in the EU.***
    - ~~*the IMP is authorised, is not modified, and is manufactured in the EU; or*~~
    - ~~*the IMP is not manufactured in the EU, but is authorised and is not modified.*~~

25. If the IMP is not authorised, and does not have a marketing authorisation from a third country that is party to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and is not manufactured in the EU, the following documentation shall be submitted:
    - a copy of the ~~*importation*~~ authorisation as referred to in Article 58; and
    - certification by the qualified person in the EU that the manufacturing complies with GMP at least equivalent to the GMP in the EU, unless there are specific arrangements provided for in mutual recognition agreements between the EU and third countries.

26. In all other cases, a copy of the ~~*manufacturing/importing*~~ authorisation as referred to in Article 58 shall be submitted.

27. For ***processes related to*** IMPs ***set out in Article 58 (5),*** ~~*the manufacturing or importation of*~~ which is not subject to an authorisation in accordance with Article 58, documentation to demonstrate compliance with the requirements referred to in Article 58(6) shall be submitted.

## ~~*7G.*~~ IMP DOSSIER (IMPD)

28. The IMPD shall give information on the quality of any IMP, the manufacture and control of the IMP, and data from non-clinical studies and from its clinical use.

~~*7.*~~*1.1. Data relating to the IMP*

~~***7.1.1.1.***~~ Introduction

29. Regarding data, the IMPD may be replaced by other documentation which may be submitted alone or with a simplified IMPD. The details of this 'simplified IMPD' are set out in section ~~*7.*~~1.2 ***"Simplified IMPD by referring to other documentation"***.

30. ***Each section of t~~T~~***he IMPD shall be prefaced with a detailed table of contents and a glossary of terms.

31. The information in the IMPD shall be concise. The IMPD must not be unnecessarily voluminous. It is preferable to present data in tabular form accompanied by a brief narrative highlighting the main salient points.

~~***7.1.1.2.***~~ Quality data

32. Quality data shall be submitted in a logical structure ***such as that of Module 3 of the Common Technical Document format***.

~~***7.1.1.3.***~~ Non-clinical pharmacology and toxicology data

33. The IMPD shall also contain summaries of non-clinical pharmacology and toxicology data for any IMP used in the clinical trial ***in accordance with international guidance***. It shall contain a reference list of studies conducted and appropriate literature references. Wherever appropriate, it is preferable to present data in tabular form accompanied by a brief narrative highlighting the main salient points. The summaries of the studies conducted shall allow an assessment of the adequacy of the study and whether the study has been conducted according to an acceptable protocol.

34. Non-clinical pharmacology and toxicology data shall be submitted in a logical structure, such as ***that ~~the headings of the current version~~*** of Module 4 of the Common Technical Document~~***, or the eCTD***~~ format.

35. The IMPD shall provide a critical analysis of the data, including justification for omissions of data, and an assessment of the safety of the product in the context of the proposed clinical trial rather than a mere factual summary of the studies conducted.

36. The IMPD shall contain a statement of the good laboratory practice status or equivalent standards, as referred to in Article 25(3).

37. The test material used in toxicity studies shall be representative of that of the clinical trial use in terms of qualitative and quantitative impurity profiles. The preparation of the test material shall be subject to the controls necessary to ensure this and thus support the validity of the study.

~~*7.1.1.4.*~~ Previous clinical trial and human experience data

38. Clinical trial and human experience data shall be submitted in a logical structure, such as ***that*** ~~***the headings of the current version***~~ of Module 5 of the Common Technical Document~~***, or of the eCTD***~~ format.

39. This section shall provide summaries of all available data from previous clinical trials and human experience with the IMPs.

40. It shall contain a statement of the GCP compliance of the clinical trials referred to, as well as a reference to the public entry referred to in Article 25(4) to (6).

~~*7.1.1.5.*~~ Overall risk and benefit assessment

41. This section shall provide a brief integrated summary that critically analyses the non-clinical and clinical data in relation to the potential risks and benefits of the ***investigational medicinal product in the*** proposed ***clinical*** trial unless this information is already provided in the protocol. In the latter case, it shall cross-refer to the relevant section in the protocol. The text shall identify any studies that were terminated prematurely and discuss the reasons. Any evaluation of foreseeable risks and anticipated benefits for studies on minors or incapacitated adults shall take account of the specific provisions set out in this Regulation.

42. Where appropriate, safety margins shall be discussed in terms of relative systemic exposure to the IMP, preferably based on 'area under the curve' (AUC) data, or peak concentration ($C_{max}$) data, whichever is considered more relevant, rather than in terms of applied dose. The clinical relevance of any findings in the non-clinical and clinical studies along with any recommendations for further monitoring of effects and safety in the clinical trials shall also be discussed.

~~*7.*~~*1.2. Simplified IMPD by referring to other documentation*

43. The applicant may refer to other documentation submitted alone or with a simplified IMPD.

~~***7.1.2.1.***~~ Possibility ~~***to***~~ ***of*** refer***ring*** to the IB

44. The applicant may either provide a stand-alone IMPD or cross-refer to the IB for the ***reference safety information and the summaries of*** pre-clinical and clinical parts of the IMPD. In the latter case, the summaries of pre-clinical information and clinical information shall include data, preferably in tables, providing sufficient detail to allow assessors to reach a decision on the potential toxicity of the IMP and the safety of its use in the proposed trial. If there is some special aspect of the pre-clinical data or clinical data that requires a detailed expert explanation or discussion beyond what would usually be included in the IB, the pre-clinical and clinical information shall be submitted as part of the IMPD.

~~***7.1.2.2.***~~ Possibility ~~***to***~~ ***of*** refer***ring*** to the SmPC

45. The applicant may submit the ~~***current***~~ version of the SmPC ***valid at the time of application*** as the IMPD if the IMP is authorised. The exact requirements are detailed in Table 1. ***Where new data is provided it should be clearly identified.***

**Table 1: Content of simplified IMPD**

| **Types of previous assessment** | **Quality data** | **Non-clinical data** | **Clinical data** |
|---|---|---|---|
| The IMP is authorised or has a marketing authorisation in an ICH country and is used in the trial: | | | |
| - within the conditions of the SmPC | SmPC | | |
| - outside the conditions of the SmPC | SmPC | If appropriate | If appropriate |
| - after modification (e.g. blinding) | P+A | SmPC | SmPC |
| Another pharmaceutical form or strength of the IMP is authorised or has a marketing authorisation in an ICH country and the IMP is supplied by the marketing authorisation holder | SmPC+P+A | Yes | Yes |
| The IMP is not authorised and has no marketing authorisation in an ICH country but the active substance is contained in an authorised medicinal product and | | | |
| - is supplied by the same manufacturer | SmPC+P+A | Yes | Yes |
| - is supplied by another manufacturer | SmPC+S+P+A | Yes | Yes |
| The IMP was subject to a previous clinical trial application and authorised in the Member State concerned and <u>has not been modified</u> and | | | |
| - no new data are available since last amendment to the CTA | Reference to previous submission | | |
| - new data are available since last amendment to the CTA | New data | New data | New data |
| - is used under different conditions | If appropriate | If appropriate | If appropriate |

(S: Data relating to the active substance; P: Data relating to the IMP; A: Additional information on Facilities and Equipment, Adventitious Agents Safety Evaluation, Novel Excipients, and Solvents for Reconstitution and Diluents)

46. If the IMP is defined in the protocol in terms of active substance or ATC code (see above, section 4), the applicant may replace the IMPD by one representative SmPC for each active substance/active substance pertaining to that ATC group. Alternatively, the applicant may provide a collated document containing information equivalent to that in the representative SmPCs for each active substance that could be used as an IMP in the clinical trial.

*~~7.~~1.3. IMPD in cases of placebo*

47. If the IMP is a placebo, the information requirements shall be limited to quality data. No additional documentation is required if the placebo has the same composition as the tested investigational medicinal product ***(with the exception of the active substance)***, is manufactured by the same manufacturer, and is not sterile.

## ***~~8H~~.*** AUXILIARY MEDICINAL PRODUCT DOSSIER

48. Without prejudice to Article 62, the documentation requirements set out in sections 6 and 7 shall also apply ***~~also for~~ to*** auxiliary medicinal products. However, where the auxiliary medicinal product is authorised in the Member State concerned, no additional information is ***~~submitted~~ required***.

## ***~~9I~~.*** SCIENTIFIC ADVICE AND PAEDIATRIC INVESTIGATION PLAN (PIP)

49. If available, a copy of the summary of scientific advice of the Agency or of any Member State or third country with regard to the clinical trial shall be submitted.

50. If the clinical trial is part of an agreed PIP, a copy of the Agency's decision on the agreement on the PIP, and the opinion of the Paediatric Committee, unless these documents are fully accessible via the internet shall be submitted. In the latter case, a link to this documentation in the cover letter is sufficient (see section ***~~2~~B***).

***~~10J~~.*** **CONTENT OF THE LABELLING OF THE IMPS**

***50a. A description of the content of the labelling of the IMP in accordance with Annex IV shall be provided.***

***~~11K~~.*** **RECRUITMENT ARRANGEMENTS (INFORMATION PER MEMBER STATE CONCERNED)**

51. Unless described in the protocol, a separate document shall describe in detail the procedures for ***~~enrolment~~ inclusion*** of subjects ***and shall provide a clear indication of what the first act of recruitment is***.

52. Where the recruitment of subjects is done through advertisement, copies of the advertising material shall be submitted, including any printed materials, and audio or visual recordings. The procedures proposed for handling responses to the advertisement shall be outlined. This includes ***~~the~~ copies of communications used to invite subjects to participate in the clinical trial and ~~planned~~*** arrangements for information or advice to the respondents found not to be suitable for inclusion in the trial.

***~~12L~~.*** **SUBJECT INFORMATION*, INFORMED CONSENT FORM* AND INFORMED CONSENT PROCEDURE (INFORMATION PER MEMBER STATE CONCERNED)**

53. All information ***given*** to the subjects (or, where applicable, ***~~the parents or~~ a*** legal***ly designated*** representative) before their decision to participate or abstain from participation shall be submitted together with the form for written informed consent.

54. ***A ~~Description~~ description*** of procedures relating to informed consent ***for all subjects, and in particular ~~in specific circumstances to be submitted~~***:

- in trials with minors or incapacitated subjects, the procedures to obtain informed consent from the parent(s) or legal***ly designated*** representative, and the involvement of the minor or incapacitated subject shall be described;
- if a procedure with witnessed consent is to be used, relevant information on the reason for using a witness, on the selection of the witness and on the procedure for obtaining informed consent shall be provided.
- in the case of clinical trials as referred to in Article 32, the procedure for obtaining the informed consent of the legal***ly designated*** representative and the subject to continue the clinical trial shall be described.
- in the case of clinical trials in emergency situations, description of the procedures followed to identify the urgency situation and to document it.
- ***in the case of clinical trials that require that groups of individual subjects rather than individual subjects are allocated to receive different investigational medicinal products where simplified means for obtaining informed consent will be used, the simplified means shall be described.***

55. In the***~~se~~*** cases ***set out in point 54***, the information given to the subject and to the ***~~parents or~~*** legal***ly designated*** representative shall be ***~~provided~~ submitted***.

## ***~~13M.~~*** SUITABILITY OF THE INVESTIGATOR (INFORMATION PER MEMBER STATE CONCERNED)

56. A list of the planned clinical trial sites, the name and position of the investigators responsible for a team of investigators conducting a clinical trial at a clinical trial site ***~~('principal investigator')~~*** and the ***planned*** number of subjects at the sites shall be submitted.

57. Description of the qualification of the ***~~principal~~*** investigators in a current curriculum vitae and other relevant documents shall be submitted. Any previous training in the principles of GCP or experience obtained from work with clinical trials and patient care shall be described.

58. Any conditions, such as economic interests ***and institutional affiliations***, that might be suspected to influence the impartiality of the ~~***principal***~~ investigators shall be presented.

**~~*14N*~~. SUITABILITY OF THE FACILITIES (INFORMATION PER MEMBER STATE CONCERNED)**

59. A ***duly justified*** written statement on the suitability of the trial sites ***adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise, issued*** by the head of the clinic/institution at the trial site or by some other responsible person, according to the system in the Member State shall be submitted.

**~~*15O*~~. PROOF OF INSURANCE COVER OR INDEMNIFICATION (INFORMATION PER MEMBER STATE CONCERNED)**

***59a. Proof of insurance cover or indemnification shall be submitted, if applicable.***

**~~*16P*~~. FINANCIAL <u>AND OTHER</u> ARRANGEMENTS (INFORMATION PER MEMBER STATE CONCERNED)**

***59b. A brief description of the financing of the clinical trial.***

60. Information on financial transactions and compensation paid to subjects and investigator/site for participating in the clinical trial shall be submitted.

61. Description of any ***other*** agreement between the sponsor and the site shall be submitted.

**~~*17Q*~~. PROOF OF PAYMENT OF FEE (INFORMATION PER MEMBER STATE CONCERNED)**

***61a. Proof of payment shall be submitted, if applicable.***

## *R. PROOF THAT DATA WILL BE PROCESSED IN COMPLIANCE WITH THE EU LAW ON DATA PROTECTION*

***61b. A statement by the sponsor or his representative that data will be collected and processed in accordance with Directive 95/46/EEC shall be provided.***

# ANNEX II

## Application dossier for substantial modification

### ~~*1A*~~. INTRODUCTION AND GENERAL PRINCIPLES

1. Where a substantial modification concerns more than one clinical trial of the same sponsor and the same ***investigational medicinal product (***IMP***)***, the sponsor may make a single request for authorisation ***of the substantial modification***. The cover letter ~~***and the notification***~~ ***shall*** contain a list of all clinical trials ~~***affected***~~ ***to which the application for substantial modification relates,*** with the~~***ir***~~ official identification numbers and respective modification code numbers ***of each of those trials***.

2. The application shall be signed by the sponsor ***or a representative of the sponsor***. This signature confirms that the sponsor is satisfied that:
   - the information provided is complete;
   - the attached documents contain an accurate account of the information available; ***and***
   - the clinical trial will be conducted in accordance with the amended documentation.

### ~~*2B*~~***B*. COVER LETTER**

3. A cover letter with the following information
   – in its subject line the EU trial number ~~***and the sponsor protocol number (if available)***~~ with the title of the trial and the ~~***sponsor's***~~ ***substantial*** modification code number ***which allows*** ~~***allowing***~~ unique identification of the substantial modification, ~~***whereby care is taken to use the code number***~~ ***and which shall be used*** consistently ***throughout the cover letter***;
   – identification of the applicant;
   – identification of the ***substantial*** modification (***the*** sponsor's substantial modification code number and date), whereby ~~***one***~~ ***the*** modification ~~***could***~~ ***may*** refer to several changes in the protocol or scientific supporting documents;

– a highlighted indication of any special issues relating to the modification and an indication as to where the relevant information or text is ***located*** in the original application dossier;
– identification of any information not contained in the modification application form that might impact on the risk to subjects;
– where applicable, a list of all ~~***affected***~~ clinical trials ***which are substantially modified,*** with ~~***official identification***~~ ***EU trial*** numbers and respective modification code numbers ~~***(see above)***~~.

## ~~*3C.*~~ MODIFICATION APPLICATION FORM

***3a. The modification application form, duly completed.***

## ~~*4D.*~~ DESCRIPTION OF THE MODIFICATION

4. The modification shall be ***presented and*** described as follows:
– an extract from the ~~***amended***~~ documents ***to be amended*** showing previous and new wording in track changes, as well as an extract showing only the new wording***, and an explanation of the changes***;
– notwithstanding the previous point, if the changes are so widespread or far-reaching that they justify an entirely new version of the document, a new version of the entire document (in such cases, an additional table lists the amendments to the documents, whereby identical changes can be grouped).

5. The new version ***of the document*** shall be identified by the date and an updated version number.

## ~~*5E*~~. SUPPORTING INFORMATION

6. ~~***Additional***~~ ***Where applicable, additional*** supporting information shall ***at least*** include ~~***where applicable***~~:

   – summaries of data;

   – an updated overall risk/benefit assessment;

   – possible consequences for subjects already included in the trial;

   – possible consequences for the evaluation of the results.

   – ***documents which relate to any changes to the information provided to subjects, the informed consent procedure, informed consent forms, information sheets, or to letters of invitation, and***

   – ***a justification for the changes sought in the substantial modification application.***

## ~~*6F*~~. UPDATE*D* ~~*OF*~~ EU APPLICATION FORM

7. If a substantial modification involves changes to entries on the EU application form ***referred to in Annex I***, a revised version of that form shall be submitted. The fields affected by the substantial modification shall be highlighted in the revised form.

# ANNEX III

## Safety reporting

### 1. REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR TO THE SPONSOR

~~*1. An adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product.*~~

~~*2. The investigator shall report the serious adverse events referred to in Article 37(2) immediately following knowledge of the serious adverse event. If necessary, a follow-up report shall be sent to allow the sponsor to determine whether the serious adverse event requires reassessment of the benefit-risk balance of the clinical trial.*~~

3. ~~*The investigator shall be responsible for reporting to the sponsor all serious adverse events in relation to subjects treated by him or her in the clinical trial.*~~ The investigator does not need to actively monitor subjects for adverse events once the trial has ended with regard to the subjects treated by him, unless otherwise provided for in the protocol.

~~*4. Serious adverse events occurring to a subject after the end of the trial with regard to the subjects treated by him shall be reported to the sponsor if the investigator becomes aware of them.*~~

## 2. REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS) BY THE SPONSOR TO THE AGENCY *IN ACCORDANCE WITH ARTICLE 38*

### 2.1. ~~*Serious event, 'reaction'*~~ *Adverse Events and Causality*

~~*5. A medical event which requires an intervention to prevent one of the characteristics/consequences referred to in point 29 of the second paragraph of Article 2 is a serious adverse event.*~~

6. ~~*The definition of*~~ ***Obligations to report*** adverse reaction***s also*** covers ~~*also*~~ medication errors***, pregnancies*** and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

7. ~~*The definition implies*~~ ***In determining whether an adverse event is an adverse reaction, consideration shall be given to whether there is*** a reasonable possibility of ***establishing*** a causal relationship between the event and the IMP ***based on the analysis of available evidence***. ~~This means that there are facts (evidence) or arguments to suggest a causal relationship.~~

8. In the absence of information on causality ~~*from*~~ ***provided by*** the reporting investigator, the sponsor shall consult the reporting investigator and encourage him to express an opinion on this aspect. The causality assessment given by the investigator shall not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor shall be provided with the report.

### 2.2. 'Expectedness'/'unexpectedness' *and the Reference Safety Information*

9. ~~*Regarding unexpectedness, reports which*~~ ***In determining whether an adverse event is unexpected, consideration shall be given to whether the event*** add***s*** significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction ~~*shall constitute unexpected events*~~.

10. The expectedness of an adverse reaction shall be ***~~determined~~ set out*** by the sponsor in the reference safety information ('RSI'). ***~~This is done from the perspective~~ Expectedness shall be determined on the basis*** of events previously observed ***with the active substance***, not on the basis of ***~~what might be~~ the*** anticipated ***~~from the~~*** pharmacological properties of a medicinal product ***or events related to the subject's disease***.

11. The RSI ***~~is~~ shall be*** contained in the Summary of product characteristics ('SmPC') or the investigator's brochure (IB). The covering letter ***~~which is submitted with the application dossier~~*** shall refer to ***the location of*** the RSI ***in the application dossier***. If the IMP is authorised in several Member States concerned with different SmPCs, the sponsor shall select the most appropriate SmPC, with reference to subject safety, as ***the*** RSI.

12. The RSI may change during the conduct of a clinical trial. For the purpose of reporting of suspected unexpected serious adverse reactions (SUSARs) the version of the RSI at the moment of occurrence of the SUSAR shall apply. Thus, a change of the RSI impacts on the number of adverse reactions to be reported as SUSARs. Regarding the applicable RSI for the purpose of the annual safety report, see section 3.

13. If information on expectedness has been ***~~made available~~ provided*** by the reporting investigator, this shall be taken into consideration by the sponsor.

~~*2.3. Detailed scope of SUSARs to be reported*~~

~~*14. The sponsor of a clinical trial performed in at least one Member State shall report the following SUSARs:*~~

- ~~*all SUSARs occurring in that clinical trial, irrespective of whether the SUSAR has occurred at a trial site in a Member State or third country concerned; and*~~
- ~~*all SUSARs related to the same active substance (regardless of pharmaceutical form and strength or indication investigated) in a clinical trial performed exclusively in a third country, if that clinical trial is*~~
  - ~~*sponsored by the same sponsor; or*~~
  - ~~*sponsored by another sponsor who is either part of the same mother company or who develops a medicinal product jointly, on the basis of a formal agreement, with that other sponsor. Provision of the IMP or information to a future potential marketing authorisation holder on safety matters should not be considered a joint development.*~~

~~*15. SUSARs identified after the end of the trial shall be reported as well.*~~

*2.3a. Information for the reporting of SUSARs*

*15a. The information shall at least include:*

- *valid EU trial number;*
- *sponsor study number;*
- *one identifiable coded subject;*
- *one identifiable reporter;*
- *one SUSAR;*
- *one suspect IMP (including active substance name-code);*
- *a causality assessment.*

***15b. In addition, in order to properly process the report electronically, the following administrative information shall be provided:***

- ***the sender's (case) safety report unique identifier;***
- ***the receive date of the initial information from the primary source;***
- ***the receipt date of the most recent information;***
- ***the worldwide unique case identification number;***
- ***the sender identifier.***

**2.4.** ~~***Time limits for reporting fatal or life-threatening***~~ ***Follow-up Reports of*** **SUSARs**

~~***16. For fatal and life-threatening SUSARs the sponsor shall report at least the minimum information as soon as possible and in any case no later than seven days after being made aware of the case.***~~

17. If the initial report ***of a SUSAR referred to in Article 38(2)(a) (fatal or life-threatening)*** is incomplete, e.g. if the sponsor has not provided all the information/assessment within seven days, the sponsor shall submit a completed report based on the initial information within an additional eight days.

18. The clock for initial reporting (day 0 = Di 0) starts as soon as the information containing the minimum reporting criteria has been received by the sponsor.

19. If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information shall be reported as a follow-up report within 15 days.

~~***2.5. Time limits for reporting non-fatal or non-life-threatening SUSARs***~~

~~***20. SUSARs which are not fatal and not life-threatening shall be reported within 15 days.***~~

21. If ***the initial report of*** a SUSAR ***referred to in Article 38(2)(c) (~~turns out to be fatal or life-threatening, whereas~~*** initially ***~~it was~~*** considered **to be** ***~~as~~*** non-fatal or ***~~not~~ non-***life-threatening***~~, the non-fatal or non-life-threatening SUSAR shall be reported as soon as possible, but within 15 days.~~ but which turns out to be fatal or life-threatening) is incomplete, a ~~The fatal or life-threatening SUSAR~~*** follow-up report shall be made as soon as possible, but within a maximum of seven days after first knowledge of the reaction being fatal or life-threatening. ***~~Regarding the follow-up report, see section 2.4.~~ The sponsor shall submit a completed report within an additional eight days.***

22. In cases where a SUSAR turns out to be fatal or life-threatening, whereas initially it was considered as non-fatal or not life-threatening, ***~~while~~ if*** the initial report has not yet been submitted, a combined report shall be created.

**2.6. Unblinding treatment allocation**

***~~23. Only SUSARs on which the treatment allocation of the subject is unblinded shall be reported by the sponsor.~~***

24. The investigator shall only unblind the treatment allocation ***of a subject*** in the course of a clinical trial if ***~~this~~ unblinding*** is relevant to the safety of the subject.

***24a. When reporting a SUSAR to the Agency, the sponsor shall only unblind the treatment allocation of the affected subject to whom the SUSAR relates.***

25. ***~~As regards the sponsor, when~~ If*** an event ***~~may be~~ is potentially*** a SUSAR the blind shall be broken ***for that individual subject only*** by the sponsor ***~~only for that specific subject~~***. The blind shall be maintained for ***other*** persons responsible for the ongoing conduct of the trial (such as the management, monitors, investigators) and those ***persons*** responsible for data analysis and interpretation of results at the conclusion of the trial, such as biometrics personnel.

***25a.*** Unblinded information shall ~~***only***~~ be accessible ***only*** to ~~***those***~~ ***persons*** who need to be involved in the safety reporting to the Agency, Data Safety Monitoring Boards ('DSMB'), or ***to*** persons performing ongoing safety evaluations during the trial.

26. However, for ***clinical*** trials ***carried out*** in high morbidity or high mortality disease, where efficacy end-points could also be SUSARs or when mortality or another 'serious' outcome (that may potentially be reported as a SUSAR) is the efficacy end-point in a clinical trial, the integrity of the clinical trial may be compromised if the blind is systematically broken. Under these and similar circumstances, the sponsor shall highlight in the protocol which serious events ~~***would***~~ ***shall*** be treated as disease-related and not subject to systematic unblinding and expedited reporting.

27. ~~***In all cases,***~~ ***If*** following unblinding, ~~***if the***~~ ***an*** event turns out to be a SUSAR ~~***(for example as regards expectedness),***~~ the reporting rules for SUSARs ***set out in Article 38 and Section 2 of this Annex*** shall apply.

3. ANNUAL SAFETY REPORTING BY THE SPONSOR

28. The report shall contain, in an appendix, the RSI in effect at the start of the reporting period.

29. The RSI in effect at the start of the reporting period shall serve as RSI during the reporting period.

30. If there are significant changes to the RSI during the reporting period they shall be listed in the annual safety report. Moreover, in this case the revised RSI shall be submitted as an appendix to the report, in addition to the RSI in effect at the start of the reporting period. Despite the change to the RSI, the RSI in effect at the start of the reporting period serves as RSI during the reporting period.

*ANNEX IIIA*

*Content of the summary of the results of the clinical trial*

***The summary of the results of the clinical trial shall contain information on the following elements:***

***A. CLINICAL TRIAL INFORMATION:***

1. ***Clinical trial identification (including title of the trial and protocol number).***
2. ***Identifiers (including EU trial number, other identifiers).***
3. ***Sponsor details (including scientific and public contact points).***
4. ***Paediatric regulatory details (including information whether the trial is a part of a Paediatric Investigation Plan).***
5. ***Result analysis stage (including information about intermediate data analysis date, interim or final analysis stage, date of global end of the trial).***
   ***For trials replicating studies on medicinal product already authorised and used in accordance with the terms of the marketing authorisation, the summary of the result should also indicate identified concerns in the overall results of the trial relating to relevant aspects of the efficacy of the related medicinal product.***
6. ***General information about the trial (including information about main objectives of the trial, trial design, scientific background and explanation of rationale for the trial; date of the start of the trial, measures of protection of subjects taken, background therapy; statistical methods used).***
7. ***Population of trial subjects (including information with actual number of subjects included in the trial in the Member State concerned, in EU and third countries; age group breakdown, gender breakdown).***

***B. SUBJECT DISPOSITION:***

1. ***Recruitment (including information with number of subjects screened, recruited and withdrawn; inclusion and exclusion criteria; randomization and blinding details; investigational medicinal products used).***
2. ***Pre-assignment Period.***
3. ***Post Assignment Periods.***

***C. BASELINE CHARACTERISTICS:***

1. ***Baseline Characteristics (Required) Age.***
2. ***Baseline Characteristics (Required) Gender.***
3. ***Baseline Characteristics (Optional) Study Specific Characteristic.***

***D. END POINTS:***

1. ***Endpoint definitions.****
2. ***End Point #1***

   ***Statistical Analyses***
3. ***End Point #2***

   ***Statistical Analyses***

****Information shall be provided for as many end points as defined in the protocol.***

***E. ADVERSE EVENTS:***

1. ***Adverse events information.***
2. ***Adverse event reporting group.***
3. ***Serious adverse event.***
4. ***Non-serious adverse event.***

***F. MORE INFORMATION:***

1. ***Global Substantial Modifications.***
2. ***Global Interruptions and re-starts.***
3. ***Limitations, addressing sources of potential bias and imprecisions & Caveats***
4. ***A declaration of the submitting party on liability for the accuracy of the submitted information.***

*ANNEX IIIB*

***Content of the summary of the results of the clinical trial for lay persons***

***The summary of the results of the clinical trial for lay persons shall contain information on the following elements:***

1. ***Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers).***
2. ***Name and contact details of the sponsor.***
3. ***General information about the clinical trial (including where and when the clinical trial was conducted, main objectives of the trial and explanation of rationale for the trial).***
4. ***Population of trial subject (including information with actual number of subjects included in the trial in the Member State concerned, in EU and third countries; age group breakdown, gender breakdown, inclusion and exclusion criteria).***
5. ***Investigational medicinal products used.***
6. ***Description of adverse reactions and their frequency.***
7. ***Overall results of the trial.***
8. ***Comments on the outcome of the trial.***
9. ***Indication if follow up trials are foreseen.***
10. ***Indication where additional information could be found.***

# ANNEX IV

# IMP and AMP labelling

## ~~*1A.*~~ UNAUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

### ~~*1A*~~.1. General rules

1. The following particulars shall appear on the immediate and the outer packaging:

(a) name, address and telephone number of the main contact for information on the product, clinical trial and emergency unblinding; this may be the sponsor, contract research organisation or investigator (for the purpose of this Annex this is referred to as the 'main contact');

***(aa) the name of the substance and its strength or potency, and in the case of blind clinical trials the name of the substance shall appear with the name of the comparator or placebo on the packaging of both the unauthorised investigational medicinal product and the comparator or placebo;***

(b) pharmaceutical form, route of administration, quantity of dosage units~~***, and, in the case of open label trials, the name/identifier and strength/potency***~~;

(c) the batch or code number identifying the contents and packaging operation;

(d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(e) the subject identification number/treatment number and, where relevant, the visit number;

(f) the name of the investigator (if not included in (a) or (d));

(g) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);

(h) 'For clinical trial use only' or similar wording;

(i) the storage conditions;

(j) period of use (~~***use-by date,***~~ expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity;

(k) 'Keep out of reach of children', except when the product is for use in trials where the product is not taken home by subjects.

2. Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings or handling instructions may be displayed.

3. The address and telephone number of the main contact ***~~need~~ shall*** not ***be required to*** appear on the label ***~~where~~ if*** subjects have been given a leaflet or card which provides these details and have been instructed to keep this in their possession at all times.

**~~1~~*A*.2. Limited labelling of immediate packaging**

~~1~~*A.2.1. Immediate and outer packaging provided together*

4. When the product is provided to the subject or the person administering the medication in an immediate package and outer packaging intended to remain together, and the outer packaging carries the particulars listed in section ~~1~~**A**.1., the following particulars shall appear on the immediate packaging (or any sealed dosing device that contains the immediate package):
   (a) name of the main contact;
   (b) pharmaceutical form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and, in the case of open label trials, the name/identifier and strength/potency;
   (c) batch and/or code number identifying the contents and packaging operation;
   (d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
   (e) the subject identification number/treatment number and, where relevant, the visit number~~.~~**;**
   ***(f) period of use (expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.***

*A.2.2. Small immediate packaging*

5. If the immediate packaging takes the form of blister packs or small units such as ampoules on which the particulars required in section ~~*1*~~*A*.1. cannot be displayed, the outer packaging ~~*is*~~ ***shall be*** provided bearing a label with those particulars. The immediate packaging shall contain the following:

(a) name of the main contact;

(b) route of administration (may be excluded for oral solid dose forms) and, in the case of open label trials, the name/identifier and strength/potency;

(c) batch or code number identifying the contents and packaging operation;

(d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(e) the subject identification number/treatment number and, where relevant, the visit number~~.~~***;***

***(f) period of use (expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.***

## ~~*2B*~~. UNAUTHORISED AUXILIARY MEDICINAL PRODUCTS

6. The following particulars shall appear on the immediate and the outer packaging:

(a) name of the main contact;

(b) name of the medicinal product, followed by its strength and pharmaceutical form;

(c) statement of the active substances expressed qualitatively and quantitatively per dosage unit;

***(ca) the batch or code number identifying the contents and packaging operation;***

(d) trial reference code allowing identification of the trial site, investigator and subject~~.~~***;***

***(e) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);***

***(f) "For clinical trial use only" or similar wording;***

***(g) the storage conditions;***

***(h) period of use (expiry date or retest date as applicable).***

## ~~*3C.*~~ ADDITIONAL LABELLING FOR AUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

7. ~~*The*~~ ***In accordance with Article 64(2), the*** following particulars shall appear on the immediate and the outer packaging:

   (a) name of the main contact;

   (b) trial reference code allowing identification of the trial site, investigator***, sponsor*** and subject~~.~~***;***

   ***(c) 'For clinical trial use only' or similar wording.***

## ~~*4D.*~~ REPLACING OF INFORMATION

8. ***The*** ~~***Any of the***~~ particulars listed in sections ~~***1, 2, and 3***~~ ***A, B and C, other than those particulars listed in point 8a,*** may be omitted ***from the label of a product*** and ~~***replaced***~~ ***made available*** by other means (e.g. use of a centralised electronic randomisation system, use of a centralised information system) provided that subject safety and the reliability and robustness of data are not compromised. This shall be justified in the protocol.

***8a. The particulars which may not be omitted from the label of a product and made available by other means are as follows:***

- ***paragraph 1, subparagraphs (aa), (b), (c), (e), (i) and (j);***
- ***paragraph 4, subparagraphs (b), (c), (e), and (f);***
- ***paragraph 5, subparagraphs (b), (c), (e), and (f);***
- ***paragraph 6, subparagraphs (b), (ca), (d), (g), and (h).***

## ANNEX V
## Correlation table

This table is subject to revision in connection with the legal-linguistic finalisation!

| Directive 2001/20/EC | This Regulation |
|---|---|
| Article 1(1) | Articles 1, 2, 1st paragraph, 2nd paragraph (1), (2), (4) |
| Article 1(2) | Article 2, 2nd paragraph (26) |
| Article 1(3), 1st subparagraph | - |
| Article 1(3), 2nd subparagraph | Article 44, 3rd subparagraph |
| Article 1(4) | Article 44, 2nd subparagraph |
| Article 2 | Article 2 |
| Article 3(1) | - |
| Article 3(2) | Article 4, 28, 29(1), 72 |
| Article 3(3) | - |
| Article 3(4) | Article 29(3) |
| Article 4 | Articles 28, 31, 10(1) |
| Article 5 | Articles 28, 30, 10(2) |
| Article 6 | Articles 4 to 14 |
| Article 7 | Articles 4 to 14 |
| Article 8 | - |
| Article 9 | Articles 4 to 14 |
| Article 10(a) | Articles 15 to 24 |
| Article 10(b) | Article 51 |
| Article 10(c) | Articles 34, 35 |
| Article 11 | Article 78 |
| Article 12 | Article 74 |
| Article 13(1) | Article 58(1) to (4) |

| | |
|---|---|
| Article 13(2) | Article 58 (2) |
| Article 13(3), 1st subparagraph | Article 59(1), 60(1), (3) |
| Article 13(3), 2nd subparagraph | Article 60(1) |
| Article 13(3), 3rd subparagraph | - |
| Article 13(4) | Article 59(2) |
| Article 13(5) | - |
| Article 14 | Article 63-67 |
| Article 15 | Article 75 |
| Article 16 | Article 37 |
| Article 17(1)(a) to (c) | Article 38 |
| Article 17(1)(d) | - |
| Article 17(2) | Article 39 |
| Article 17(3)(a) | - |
| Article 17(3)(b) | Article 40(1) |
| Article 18 | - |
| Article 19, 1st paragraph, 1st sentence | Article 71 |
| Article 19, 1st paragraph, 2nd sentence | Article 70 |
| Article 19, 2nd paragraph | Article 88 |
| Article 19, 3rd paragraph | - |
| Article 20 | - |
| Article 21 | Article 84 |
| Article 22 | - |
| Article 23 | - |
| Article 24 | - |