SIOP Europe's Response to the draft European Parliament legislative resolution (10/06/2013) of the EU Clinical Trial Regulation

CONTRIBUTORS:

Pamela Kearns, Vice-Chair, European Clinical Research Council for Paediatric Oncology (ECRC)
School of Cancer Sciences, University of Birmingham

Ruth Ladenstein, SIOP Europe Past-President, ENCCA Project Coordinator, Chair, ECRC
St. Anna's Children's Hospital and Children's Cancer Research Institute, Vienna, Austria

Gilles Vassal, SIOP Europe President
Institut Gustave Roussy, Villejuif, France

SIOP Europe, the European Society for Paediatric Oncology (SIOPE) continues to support the proposed Clinical Trials Regulation's stated goal to increase the feasibility to deliver academic-investigator driven clinical trials across Europe while maintaining high-quality science, patient safety and data integrity. There are three key areas on which we have focussed in the following document, which we believe to be crucial to the success of Regulation.

1. **Definition of low risk/intervention clinical trials**

   The concept of proportionate regulation of clinical trials based on a risk assessment is one of the most important initiatives within the clinical trial regulation and therefore the definition of the 'low intervention' trial (in the new proposed terminology 'low risk') category needs to capture the correct cohort of trials. The proposed European Parliament amendments (1, 9, 10, 58) propose terminology that would exclude almost every cancer trial that involves a drug intervention as there are a very few examples of chemotherapy that are associated with no or only temporary adverse effects. The crucial determinant of the risk assessment of a trial is the **relative or additional risk of the trial intervention compared to normal clinical practice, ie the treatment a trial participant would receive if not participating in the**

trial. We would strongly advocate the definition previously proposed by the European Parliament Rapporteur which captured this concept of relative or additional risk (see below)

2. **Safety Reporting**

There are two specific areas of safety reporting that remain a concern for the paediatric oncology community within the Clinical Trials Regulation.

- **Simplified submission of the annual safety report by the sponsor.** The Clinical Trials Regulation will now specify that the annual safety report is not submitted for authorised investigational medicinal products that are used within their authorised indication. For these products, the normal pharmacovigilance rules will apply (Amendment 198). We contend that for authorised products used outside the authorised indication, ie off-label but are being used within a standard treatment approach in the given protocol, this same principle should apply (Childhood Cancer Research Jeopardised unless EU Regulation is clarified)

    - **The inclusion of auxiliary medicinal products in the definition of a serious adverse reaction.** This amendment has been proposed (amendments 199 and 289) and no justification has been given. Auxiliary medicinal products are by definition not the **medicinal product under investigation**[1]. Should safety issues, including SUSARs, arise due to an interaction between the auxiliary medicinal products and the investigational medicinal product, they would be captured through the existing pharmacovigilance reporting for investigational medicinal product. The addition of a 'SUSAR' for auxiliary medicinal products does not increase the protection of patients, nor the knowledge of the safety profile of the investigation medicinal products being tested and adds excessive and unnecessary bureaucracy. In addition, will require changes the definition of a Serious Adverse Reactions and SUSARs, which currently refer to events that are attributable to the investigational medicinal product in a trial.

3. **National Indemnity Schemes**

SIOPE continues to strongly support the establishment of National Indemnity Schemes. Currently the costs of insurance premiums for non-commercial trials are met by the academic institutions (Universities and Hospitals) who are acting as Sponsor for these non-

[1] When the use of medicinal products outside of the marketing authorisation is supported by sufficient published evidence and /or standard treatment guidelines, these medicinal products should not automatically fall under the definition of an investigational medical product as they represent not products under investigation by definition. The IMP definition clearly should be limited to a specific medicinal product being subject of a trial specific research question, but should not be imposed on the majority of drugs used in the settings of rare diseases, including i.e. rare cancer entities where off-label use is part of standard treatment guidelines and hence a standard requirement.

commercial trials as the pharmaceutical industry has no interest in running trials for these rare disease patients. The costs can be prohibitive and deter academic institutions from taking on this role. A major issue is National indemnity laws differ across Member States adding to the complexity of providing cover for international studies.
Recent experiences of European Paediatric Oncology Study Groups reflect the dimension of the problem well and demonstrate how the obligatory insurance/indemnity has substantially increased the costs of conducting clinical trials, without evidence that the number of damages, or the amount, has increased with the entry into force of the Directive.
The Acute Lymphoblastic Leukemia Study Group (ALL BFM) expects a total of 2000 patients in their most recent Phase 3 international investigator driven trial (IDCT). Within Germany 400 patients will be recruited and the insurance fee only for Germany amounted to 470.000€. Another international phase 3 ALL Study exploring preparative regimens for stem cell transplantation will recruit 1000 patients where the insurance fee was 500.000€ on first offer and the final best offer was ultimately 300.000€. A phase 3 antibody trial in neuroblastoma had to cover insurance fees of 240.000€ for 400 patients.
The recent experience of a UK university sponsoring international studies is for each trial sponsored there is a minimum insurance cost of 7000 Euros per country participating in the trial, regardless of the risk assessment for the study.
Moreover, we have confirmed that no claims in relation to drug trials in the academic sector have been made. Cumulatively, these fees are a substantial addition to the costs of trial sponsorship and a major deterrent to publically-funded institutions acting as sponsors for clinical trials conducted in multiple- EU member states.

Additional Comments

- **The EU portal** for document exchange is a major technical ambition for the CTR and the infrastructure to support this must be robust and in place before the CTR is implemented.

- **The selection of the reporting Member State for multi-country trials**: we seek clarification as to how selection will be made and whether any guidance will be made available to explain the process.

- **Rare and ultra-rare diseases:** We support the new amendments that advocate that the assessment procedures should take into consideration of the challenges of undertaking trials in the life-threatening and debilitating diseases and rare and ultra-rare diseases for which there are limited existing treatment options (for example amendments 92, 94 and127).

More detailed comments on the proposed amendments are outlined below. In addition appendix 1 lists specific amendments that we strongly endorse and hope will be retained in the final version

SIOP Europe
the European Society for Paediatric Oncology

SPECIFIC COMMENTS ON PROPOSED AMENDMENTS TO CTR				
Amendment number and Article reference	**Page in CTR**	**Text proposed by the Commission**	**Amendment suggested by Parliament**	**SIOP-E preferred text**
Amendment 9 **Proposal for a regulation** **Recital 9**	**17**	(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) 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	(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) and where the intervention poses only very limited additional risk tothe subject compared to normal clinical practice. Those ***"low-risk*** 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. ***Given that***	(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) and where the intervention poses only very limited additional risk to the subject compared to normal clinical practice. Those ***"low-risk*** 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. ***Given that low-risk clinical trials have only limited additional risk compared to normal***

		health. They should be subject to less stringent rules, such as shorter deadlines for approval	***low-risk clinical trials have only a very limited and temporary adverse effect – if any – on the subject's health,*** they should be subject to less stringent rules, such as shorter deadlines for approval. ***Less stringent rules should not compromise scientific standards and should guarantee the safety of subjects at all times. Those low-risk trials should, however, be subject to the vigilance and traceability rules governing normal clinical practice***	***clinical practice,*** they should be subject to less stringent rules, such as shorter deadlines for approval. ***Less stringent rules should not compromise scientific standards and should guarantee the safety of subjects at all times. Those low-risk trials should, however, be subject to the vigilance and traceability rules governing normal clinical practice***
Article 2 – paragraph 2 – point 3 – introductory part	**26**	(3)'Low-intervention clinical trial': a clinical trial which fulfils all of the following conditions:	(3) '***Low-risk*** clinical trial': a clinical trial ***which, given the nature and extent of the intervention, can be expected to have only a very small and temporary or no impact on the subject's health*** and which fulfils all of the following conditions:	(3)'**Low-risk** clinical trial': a clinical trial which fulfils all of the following conditions:
		Justification		
Whilst we have no objection to the Parliament's change of terminology from 'low intervention' to 'low risk', the success of the Clinical Trials Regulation in introducing proportionate regulation of clinical trials according to the risks they pose to patients pivots on the definition of this category. The Parliament has proposed an amendment to the definition based on an intervention having '***only a very limited and temporary adverse effect – if any – on the subject's health'***. This definition could be interpreted to exclude any trial that uses a drug intervention. In the context of cancer treatments, all chemotherapy drugs used according to normal clinical practice will have side effects, some of which are long-term and therefore when these drugs are used to answer treatment improvement questions in a clinical trial, it will not be possible to classify the trial as low--risk, even though they drugs are used in normal clinical practice to treat a life-threatening disease such as cancer. In assessing whether a				

trial should be categorised as low risk it is the 'additional' risk to the patient over and above normal clinical practice and the threat of the disease itself,that should be assessed.

This point is illustrated by a clinical trial for childhood acute lymphoblastic leukaemia where the trial is comparing the UK normal clinical practice for consolidation treatment with the German (I-BFM) normal clinical practice. The survival outcome for both treatments is equivalent but they have never been directly compared in a clinical trial. The German treatment involves less interventions and hospitalisations for treatments and is less prolonged and therefore has the potential for improved quality-of-life for patients on treatment with the same outcome. We would assess this trial as low risk since all the interventions are within normal clinical practice but we could not state that the interventions have '***only a very limited and temporary adverse effect – if any – on the subject's health'.*** In cancer treatment this would not be possible: all chemotherapy drugs are associated with adverse effects and some of these effects are not temporary, however the effects are also part of normal clinical practice. The key point is that in assessing risk, it is the '***additional risk'*** that should be considered.

Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment by Parliament***	***SIOP-E preferred text***
Amendment 13	**72**	-	(9d) (NEW): An investigational medicinal product is an active ingredient in a pharmaceutical or placebo form tested **or used as a reference** in a clinical trial, including a medicinal product which is covered by a marketing authorisation but which is used off-label or in accordance with the current clinical practice.	An investigational medicinal product is an active ingredient in a pharmaceutical or placebo form tested in a clinical trial, including a medicinal product which is covered by a marketing authorisation but which is used off-label or in accordance with the current clinical practice.
Reference arms by definition are standard treatment arms, i.e. in low risk trial, with an already existing history of the authorised medicinal products in use even if in off-label use status. If reference medicinal products are categorised as IMP in phase 3 IDCT (up to 10 medicinal products or more in pediatric oncology standard treatment arms!) the reporting burden in ASR /DSUR will be enormous, as most of these drugs are off-patent with no or minimal likeliness of widening the label. Comparing two standard treatments in the low risk setting should not push all medicinal products into investigational medicinal product status. AMENDMENT 9e (NEW) gives a clear definition on Auxilliary Medicinal Products, i.e. use as back ground treatment and the definition should constantly apply throughout the text.				
Amendment	**26**	(a) the investigational medicinal	(a) the investigational medicinal	(a) the investigational medicinal

59 **2 part 3a**		products are authorised;	products, **or the placebos**, are authorised for **marketing and tested in accordance with their marketing authorisation;**	products **or the placebos** are authorised for **marketing**
Amendment 60 **2 part 3b**	**26**	(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 use is **a** standard **treatment in any of the Member States concerned;**	(b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing **authorisation in any of the Member States concerned or, where the use of a medicinal product is outside the terms of the marketing authorisation, their use is supported by sufficient published evidence and/or standard treatment guidelines;**	b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing **authorisation in any of the Member States concerned or, where the use of a medicinal product is outside the terms of the marketing authorisation, their use is supported by sufficient published evidence and/or standard treatment guidelines;**
Justification				
Amendment 59: Article 2 part 3a adds unnecessary text to the clause 3 which creates confusion to the definition: A) The low-risk trial is defined by three clauses in article 2 part 3; a, b and c. In clause a, the requirement for the drugs to be authorised is clearly stated and the concept of whether they are used within their marketing authorisation is addressed in clause b. The additional text to clause a proposed by the parliament would now contradict clause b. B) The justification given for the Parliamentary amendment to exclude authorised drugs not used within their marketing authorisation from the definition of low-risk trials is that this they would be considered as 'medium-risk trials'. This does not make any sense because there is no concept of a medium-risk trial within any version of the proposed Clinical Trials Regulation. Throughout the proposed Clinical Trials Regulation, the concept of 'a low-risk trials including authorised medicinal products used 'off-label' if this is supported by evidence that this is consistent with normal clinical practice' is already accepted; for example the text in in amendment 60). We have previously provided			

detailed statement on the need to acknowledge the 'off label' use of medicinal products in the Clinical Trial Regulation (Childhood Cancer Research Jeopardised unless EU Regulation is clarified).

Amendment 60: Article 2 part 3b

C) We are wholly supportive of the revised text in Article **2 part 3b** as this addresses the issue of the normal clinical practice of using drugs in an off-label setting.

Amendment and Article Reference	***Page in CTR***	***Text proposed by the Commission***	***Suggested Amendment by Parliament***	***SIOP-E preferred text***
Amendment 62 **Article 2 – paragraph 2 – point 4** ***(we believe this should refer to paragraph 4)***	**26**	(4) 'Non-interventional study': a clinical study other than a clinical trial;	(4) 'Non-interventional study': a clinical study other than a clinical trial, **which which fulfils all of the following conditions:** **(a) the medicinal product or products are prescribed in the usual way in accordance with the terms of the marketing authorisation;** **(b) the assignment of the subject to a particular therapeutic strategy is not decided in advance by a research protocol and falls within usual practice;** **(c) the decision to prescribe the medicinal product is clearly dissociated from the decision to include the patient in the clinical study;**	(4) 'Non-interventional study': a clinical study other than a clinical trial, **which which fulfils all of the following conditions:** **(a) the medicinal product or products are prescribed in the usual way in accordance with the terms of the marketing authorisation or, where the use of a medicinal product is outside the terms of the marketing authorisation , their use is supported by sufficient published evidence and/or standard treatment guidelines;** **(b) the assignment of the subject to a particular therapeutic strategy is not decided in advance by a research protocol and falls within usual**

			(d) the patients are not subject to any additional diagnostic or monitoring procedures; **(e)epidemiological methods are used to analyse the data gathered;**	**practice;** **(c) the decision to prescribe the medicinal product is clearly dissociated from the decision to include the patient in the clinical study;** **(d) the patients are not subject to any additional diagnostic or monitoring procedures;** **(e)epidemiological methods are used to analyse the data gathered;**
Justification				
The additional text proposed by the Parliament is very helpful in fully clarifying the definition of a non-interventional clinical trial. However to be consistent with the definitions throughout the Regulation, the situation where the use of medicinal products outside their marketing authorisation is according to documented normal clinical practice should be taken into account. We therefore propose additional text to clarify this point				
Amendment and Article Reference	***Page in CTR***	***Text proposed by the Commission***	***Suggested Amendment by Parliament***	***SIOP-E preferred text***
Amendment 176 Article 31 – paragraph 1 – point a (new)	***47/48***		(aa) the informed and express consent of the minor has been obtained, where they are 12 years old and over,	*We propose the new text is removed*
Amendment	**47/48**	The minor shall take part in the	The minor shall take part in the consent	The minor shall take part in the consent

185 Proposal for a regulation Article 31 – paragraph 2		consent procedure in a manner adapted to his or her age and maturity.	procedure in a manner adapted to his or her age and maturity. **Minors who are 12 years old and over shall also give their informed and express consent to participate in the clinical trial**	procedure in a manner adapted to his or her age and maturity. *We propose the new text is removed*
Amendment 186 Proposal for a regulation Article 31 – paragraph 2 a (new)	**47/48**		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	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 **he/she continues as a participant in the trial**

Justification

Amendment 176; Article 31 – paragraph 1 – point a (new) and Amendment 185; Proposal for a regulation Article 31 – paragraph 2: The age at which a minor is able to give truly informed consent is dependent on the individual child. The capacity for some minors to fully comprehend what is involved in participating in clinical trials to the same extent as an adult is highly individual, particularly between 12-16 years old, where the level of maturity and intellectual capacity is very variable. This amendment will mandate the legal age of consent to participate in a clinical trial as 12 years old and will lead to the situation of consent being required from minors who cannot reasonably be expected to be responsible for the decision to give or refuse consent. In the context of paediatric oncology trials, parents and guardians of young people with cancer have expressed their deep concerns regarding this amendment and are strongly opposed to its inclusion.

National laws currently determine both the legal age to be able to give consent to medical treatment and the legal age to consent to participate in a clinical research. These laws differ between Member States; for example; in the UK, the age at which a young person can consent to participate in a clinical trial is 16 years and in Belgium it is 18 years. In all cases, the national legislation emphasises the need for minors to be involved as much as possible in the consent process taking into account his age and maturity. We agree that wherever possible, all children should be provided with information regarding the trial in age-appropriate language. Moreover, it is good practice to obtain their **assent**, confirming their willingness to participate in the clinical trial. We do support the principle of confirming assent for minors who are competent to understand the trial.

Amendment 186 Proposal for a regulation Article 31 – paragraph 2 a (new): We support consent being obtained from minors when they reach

the age of majority according to the law of the Member State but the text of amendment 186 needs to be revised to clarify that it is for their participation in the trial to be continued and not the continuation of the whole trial.				
Amendment and Article Reference	***Page in CTR***	***Text proposed by the Commission***	***Suggested Amendment by Parliament***	***SIOP-E preferred text***
Amendment 198 Article 37 – paragraph 2 a (new)	***50***		2a. In the case of low-risk clinical trials the protocol may stipulate that the normal rules on pharmacovigilance shall apply.	
Justification				
We are supportive of the addition of this text but seek clarification that 'normal rules on pharmacovigilance' refers to normal safety reporting that applies to drugs used outside the context of a clinical trial.				
Amendment and Article Reference	***Page in CTR***	***Text proposed by the Commission***	***Suggested Amendment by Parliament***	***SIOP-E preferred text***

Amendment 201 **Article 39 – paragraph 1**	***50***	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.	***The sponsor shall submit annually by electronic means to the Agency a report on the safety of each investigational medicinal product - or of all the investigational medicinal products – used in a clinical trial for which it is the sponsor if the clinical trial involves authorised investigational medicinal products being tested in accordance with treatment strategies which were not envisaged under the terms of their marketing authorisation and which are not supported by data or recommendations and if the clinical trial involves a high level of risk.***	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 and the authorised investigational medicinal products fulfil <u>all</u> of the following: ***a. They are being tested in accordance with treatment strategies which were not envisaged under the terms of their marketing authorisation*** ***b. Their use is not supported by data or recommendations for use in normal clinical practice*** ***c. The clinical trial involves a high level of risk.***
Justification				
We believe the purpose of this amendment was to ensure annual safety reports are mandated in circumstances where there is not already existing safety data to support the way the investigational medicinal products are being used in the trial. We concur with this principle captured but the text in the proposed amendment from the European Parliament could be clearer and have therefore suggested alternative wording to help clarify this text.				
Amendment and	***Page in***	***Text proposed by the Commission***	***Suggested Amendment by Parliament***	***SIOP-E preferred text***

Article Reference	***CTR***			
Amendment 209 ***Article 41 – paragraph 1***	***51***	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.	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 ***Agency*** of all suspected serious adverse reactions, ***where relevant, those reactions concerning a specific gender or age group.***	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 ***Agency*** of all suspected **unexpected** serious adverse reactions, ***where relevant, those reactions concerning a specific gender or age group.***
Justification				
To add to the data already held by the Agency, there should be reporting of serious adverse reactions that have not been previously expected or reported for the investigational medicinal product. There is no additional useful data for the Agency in the reporting of all serious adverse reactions which are expected events. These will be collected as part of the trial data and included in the final clinical trial report.				
Amendment and Article Reference	***Page in CTR***	***Text proposed by the Commission***	***Suggested Amendment by Parliament***	***SIOP-E preferred text***
Amendment 199 ***Article 38 – paragraph 1***	***50***	1. The sponsor 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	1. The sponsor 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 **and**	1. The sponsor 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 ~~***and***~~

		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.	**auxiliary** 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 ***in accordance with the time limits set out in Annex III, points 2.4 and 2.5.***	~~***auxiliary***~~ 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 ***in accordance with the time limits set out in Annex III, points 2.4 and 2.5.***
Amendment 289 ***Annex III – part 2 – point 7***	***79***	7. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.	7. The definition implies a reasonable possibility of a causal relationship between the event and the IMP ***and/or the auxiliary medicinal product.*** This means that there are facts (evidence) or arguments to suggest a causal relationship.	7. The definition implies a reasonable possibility of a causal relationship between the event and the IMP ~~***and/or the auxiliary medicinal product.***~~ This means that there are facts (evidence) or arguments to suggest a causal relationship.

Justification

No justification has been presented for the change in the definition of a Serious Adverse Reaction and therefore the addition of reporting suspected unexpected serious adverse reactions (SUSAR) relating to auxiliary medicinal products. Auxiliary medicinal products are by definition not the medicinal product under investigation. Should safety issues, including SUSARs arise due to an interaction between the auxiliary medicinal products and the investigation medicinal product, they would be captured through the existing pharmacovigilance reporting for investigation medicinal product. The addition of a 'SUSAR' for auxiliary medicinal products does not increase the protection of patients, nor the knowledge of the safety profile of the investigation medicinal products being tested and adds excessive and unnecessary bureaucracy. In addition, will require changes in the definitions of Serious Adverse Reactions and SUSARs, which currently refer to events that are at least possibly attributable to the investigational medicinal product in a trial.

APPENDIX 1

We are supportive of many of the other proposed amendments but specifically strongly advocate that the following amendments are retained:

Amendment and Article Reference	***Page in CTR***	***Text proposed by the Commission***	***Suggested Amendment by Parliament***
Amendment 12 Proposal for a regulation Recital 9 c **(new)**	**17**		***The concept of 'Normal Clinical Practice' is of vital importance in determining whether an application is authorised as a 'low-risk clinical trial'. The definition of 'Normal Clinical Practice' should be clarified by the Commission in guidelines.***
Proposal for a regulation Recital 10 b (new)	**17**		***(10b) Experience with Directive 2001/20/EC has also shown that 60% of clinical trials are sponsored by the pharmaceutical industry and 40% by other stakeholders, such as academics. The value of academic contribution should be duly recognised by Member States. Academic sponsors frequently rely on funding which partly or entirely comes from the public funds or charities. In order to maximize the use of this valuable contribution and to further stimulate academic research but without any discrimination towards the quality of trials, measures should be put in place by Member States to make appropriate exemptions from fees (application fees, inspection fees etc...) for trials conducted by academic sponsors.***
Amendment 24 Recital 12 b (new)	**17**		***(12b) Whereas most clinical trials are conducted for***

			the assessment of therapies, targeted at large patient populations, and involving a large sample of patient populations, this Regulation should not discriminate against patients suffering from rare and ultra-rare diseases, and should integrate the specificities of low prevalence conditions into the assessment of a trial.
Amendment 51 Proposal for a regulation Recital 60	**24**	Without prejudice to the national systems for the cost and reimbursement of medical treatments, subjects should not have to pay for investigational medicinal products.	Without prejudice to the national systems for the cost and reimbursement of medical treatments, subjects should not have to pay for investigational medicinal products. ***For low-risk trials and when marketing authorisation is not the initial objective of the investigator-initiated trial, the cost of the investigational medicinal product should be borne by the national healthcare system.***
Amendment 52 Proposal for a regulation Recital 62 a (new)	**24**		***According to the Commission Communication on "An Integrated Industrial Policy for the Globalisation Era-Putting Competitiveness and Sustainability at Centre Stage", systematic evaluation of legislation should become an integral part of smart regulation. To ensure that this Regulation keeps pace with scientific, technological and medical progress with regard to the organization and conduct of clinical trials and that it interfaces with other legal provisions, the Commission should periodically report on the experience with and functioning of this Regulation, and present its conclusions to the European Parliament and to the Council.***
Amendment 56	**25**	Referring to definition of a clinical trial	

Article 2– paragraph 2 – point 2 – point b		(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;	(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***; and their use does not fall within normal clinical practice;***
Amendment 60 Article 2 – paragraph 2 – point 3 – point (b)	**26**	Referring to definition of a low intervention clinical trial (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 use is a standard treatment in any of the Member States concerned;	(b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorisation in any of the Member States ***concerned or, where the use of a medicinal product is outside the terms of the marketing authorisation, their use is supported by sufficient published evidence and/or standard treatment guidelines;***
Amendment 193 Article 34 – paragraphs 3 and 3 a	**49**	3. Within one year from the end of a clinical trial, the sponsor shall submit to the EU database a summary of the results of the clinical trial. However, where, for scientific reasons, 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 an explanation.	***3. Irrespective of the outcome of the clinical trial,*** within one year from the end of a clinical trial or from its early termination, the sponsor shall submit to the EU database a summary of the results of the clinical trial ***in accordance with Annex IIIa. It shall be accompanied by a summary presented in terms that are easily understandable to a layperson.*** However, where, for scientific reasons, 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 an ***justification***

			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 sponsor 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 sponsor has decided not to submit an application for marketing authorisation. In the event of non-compliance by the sponsor with the obligations referred to in this paragraph, financial penalties shall be imposed on the sponsor by the Member States concerned. The penalties shall be effective, proportionate and dissuasive. ***3a. The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to define the content and structure of the layperson's summary. The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to establish rules for the communication of the clinical study report.*** ***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.***
Amendment 226 Article 64 –	**58**	1. Authorised investigational medicinal products and authorised auxiliary medicinal products shall	1. Authorised investigational medicinal products and authorised auxiliary medicinal products shall ***not carry***

paragraph 1 – introductory part		be labelled	***any additional labelling.***
Amendment 230 Article 69 – paragraph 2 – introductory wording	**59**	2. By way of derogation from paragraph 1, all sponsors shall be responsible for establishing one sponsor responsible for each of the following:	2. By way of derogation from paragraph 1, all sponsors shall be responsible for establishing one sponsor ***or more*** responsible for each of the following:
Amendment 231 Article 69 – paragraph 2 – point b	**59**	(b) providing responses to all questions from subjects, investigators or any Member State concerned regarding the clinical trial;	(b) providing responses to all questions from subjects, investigators or any Member State concerned regarding the clinical trial. ***In meeting this obligation the sponsor may delegate tasks as required, in accordance with the second paragraph of Article 68;***
Amendment 235 Article 72	**60**	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.	***For low-risk clinical trials, Member States shall ensure that damage compensation is covered by the general compensation system established under the national social security or health care system*** For clinical trials other than ***low-risk*** 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. ***Adequate and comprehensive information shall be provided to the subject on the limits and conditions of damage compensation, and the conditions of use of the national indemnification mechanism referred to in Article 73***
Amendment 237 Article 75 – paragraph 3 a (new)	**61**		***Text proposed by the Commission Amendment 3a. Inspections fees, if any, shall be waived for non-commercial sponsors.***
Amendment 254 Article 82 – paragraph 1	**64**	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.	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-profit clinical trials.***
Amendment 258 Article 91 a (new)	**66**		***Five years after the entry into force of this Regulation, 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.
Amendment 283 Annex I – part 7 – point 45 – introductory part	**74**	45. The applicant may submit the current version of the SmPC as the IMPD if the IMP is authorised. The exact requirements are detailed in Table 1.	45. The applicant may submit the current version of the SmPC as the IMPD if the IMP is authorised. If a ***clinical trial is low-risk and concerns an IMP for which the treatment strategies are based on published data and/or standard treatment recommendations issued by learned societies or official bodies. The exact requirements are detailed in Table 1.***
Amendment 290 Annex III a (new)	**82**		***Annex IIIa*** ***Content of the summary of the results of clinical trials*** ***The summary of the results of the clinical trials referred to in Article 34(3) shall contain information on the following elements:*** ***1. Trial information:*** ***a) Study identification*** ***b) Identifiers*** ***c) Sponsor details*** ***Paediatric regulatory details*** ***e) Result analysis stage*** ***f) General information about the trial including: a structured summary of trial design, methods, results,***

			and conclusions; scientific background and explanation of rationale; specific objectives or hypotheses ***g) Population of trial subjects with actual number of subjects included in the trial and the eligibility criteria*** ***2. Subject disposition with sufficient details to allow for replication, including:*** ***a) Recruitment*** ***b) Pre-assignment Period*** ***c) Post Assignment Periods*** ***3. Baseline Characteristics:*** ***a) Baseline Characteristics (Required)*** ***Age*** ***b) Baseline Characteristics (Required)*** ***Gender*** ***c) Baseline Characteristics (Optional)*** ***Study Specific Characteristic*** ***4. End Points:*** ***a) Endpoint definitions*** ***b) End Point #1**** ***Statistical Analyses*** ***c) End Point #2,*** ***Statistical Analyses*** ****Information shall be provided for as many end points as defined in the protocol.*** ***5. Adverse Events:*** ***a) Adverse events information*** ***b) Adverse event reporting group*** ***c) Serious Adverse Events*** ***d) Non-serious adverse event*** ***6. More Information:*** ***a) Global Substantial Modifications*** ***b) Global Interruptions and re-starts***

			c) Limitations, addressing sources of potential bias and imprecisions, & Caveats ***7. The protocol and its subsequent modifications.***