SIOP Europe's Proposed Amendments to the EU Clinical Trials Regulation

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There are 2 major principles in this legislation that should be taken into consideration:

- Clinical trial legislation within the EU addresses clinical trials in the abstract, i.e. independently from whether the results are intended to be used in a future marketing authorisation application, or for any other purpose (e.g. improvement of treatment strategies, comparing treatment with different medicines, etc.). This difference is usually discussed under the pattern 'commercial' vs. 'academic' clinical trials. The latter form approximately 40% of clinical trials applied for in the EU. It is in particular these 'academic' clinical trials, which the proposed Clinical Trials Regulation (CTR) wants to stimulate.

- The risk to subject safety in a clinical trial mainly stems from two sources: the investigational medicinal product and the intervention. Many clinical trials 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. This type of "low-intervention clinical trial" is often of crucial importance to evaluate and improve standard treatments and diagnostic techniques, 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, such as shorter deadlines for approval.

Article	*Page*	*Text proposed by the Commission*	*Suggested Amendment*
2 part 2b	**25**	'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;	'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 **AND their use does not fall within normal clinical practice** (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;
		Justification	
		The proposed text in Article 2b to define a 'Clinical trial' would mean that any clinical study including drugs that are used outside their marketing authorisation would be defined as a clinical trial. Many standard treatment protocols use medications outside their marketing authorisation; therefore the Article could be interpreted to mean that if an observational clinical study is undertaken and data collected on patients treated according to a standard treatment protocol that includes drugs used outside its marketing authorisation, this would be defined as a clinical trial. This has the potential of bringing many more studies under the definition of the clinical trial than we believe was intended by the revision. We therefore propose that Article 2 part 2b could be clarified by the addition of a sentence to the definition, which would mean that the definition of 'clinical trial' does not apply to studies collecting data on the **standard** off-label use of medicinal products.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
2 part 3b	**26**	(3) 'Low-intervention clinical trial': a clinical trial which fulfils all of the following conditions: (a) the investigational medicinal products 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 use is a standard treatment 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	(3) 'Low-intervention clinical trial': a clinical trial which fulfils all of the following conditions: (a) the investigational medicinal products 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 **where the use of a medicinal product is outside the terms of the** marketing authorisation **but their use is supported by sufficient published evidence and/or standard treatment guidelines** (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the

		in any Member State concerned.	subjects compared to normal clinical practice in any Member State concerned.
		Justification 1	
		The 'low-intervention clinical trial' category in the CTR is a very welcome step forward allowing proportionate application of regulatory control over clinical trials. In many rare diseases, including paediatric oncology, the drugs used in their treatment are nearly always being used as standard practice outside their marketing authorisation ('off-label use'). We remain very concerned that there will be fundamental differences between Member States in applying the definition of a 'low-intervention clinical trial' when the trial includes 'off-label use' of licensed medicinal products, even when that use is standard practice outside the clinical trial. For example, individual Member States may require different levels of supporting evidence to define a treatment regimen as standard treatment in the 'off-label' drug use setting. To avoid potential diversity in interpretation, we propose: **A:** A clear guideline for the definition of standard practice in disease groups, i.e. stating the acceptable level of evidence demonstrated either through published treatment guidelines or published results of good clinical practice (GCP)-compliant clinical trials in peer-reviewed international journals. It is recognised that standard treatments are not homogenous across Europe, and acknowledge that more than one standard practice may apply for the same disease. However, to protect participants in clinical trials, it is important that a minimum of quality requirements is defined for stating that an off-label use of a drug is standard practice. An additional beneficial outcome of setting a standard requirement for this definition may be the facilitation of trials aimed at treatment optimisation: i.e., it may foster the generation of evidence-based definitions of standard practice through comparison of different standard treatments within the low intervention clinical trial' category. This will contribute to harmonisation of standard practice across Europe. **B:** We also propose a modification to the text as is shown in the adjacent column to reduce the possibility of misinterpretation **C:** We propose the sponsor should be responsible for providing the **supporting published evidence and/or national standard treatment guidelines for the medicinal products to be** defined as standard treatment for a **given indication**
Article	***Page***	***Justification 2***	
2 parts 3 and 5	**26**	**ADDITIONAL COMMENT ON DEFINING A LOW-INTERVENTIONAL TRIAL** In clinical trials where two (or more) standard practice treatment regimens are being compared, the trial does not generate any new safety information about the drugs involved. Nevertheless, under the current Directive and the proposed CTR, all drugs in both arms are defined as investigational medicinal products. To ensure that the administrative oversight of this type of trial is proportionate to the risk to the patient, it is particularly important that this type of trial is categorized within the low interventional	

		trial category. If the trial is deemed to fall outside this category, there will continue to be a disproportionate burden of drug accountability, safety reporting and insurance needs (although the latter will be mitigated to some extent by the proposed national indemnifications schemes). ***We propose that the CTR should specify that if trial treatment arms do not contain any unlicensed drugs AND ONLY compare standard practice treatment approaches then regardless of whether the drugs are being used off-label, the trial would always be categorised within the low-interventional trial category***.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
2 part 5	**26**	'Investigational medicinal product': a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial;	'Investigational medicinal product': a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial **unless its use as a reference falls within normal clinical practice**
		Justification	
		(A 'reference' in this context means the standard or usual treatment against which the new treatment regime is being tested to see if the new treatment regime is better than the standard treatment) We propose that medicinal products used according to normal clinical practice should not be upgraded to 'Investigational medicinal products' when serving as a reference in a clinical trial. The upgrading to investigational medicinal product means that enhanced and unnecessary reporting requirements will apply to these drugs; i.e. Development Safety Update Reports, drug accountability and insurance needs for drugs with already very established and known toxicity profiles as they are already part of standard practice. It has been argued that the collection of safety data on drugs used in an off label setting will contribute to modification of their labelled indication. However, the majority of these off-label drugs are already off - patent. This means that there is no longer any specific driving interest of a pharmaceutical company to consider modification of the label on the basis of such reporting (DSUR). It is essential to address this heavy workload, which falls predominantly on academia but is meaningless as the information does not add to current knowledge and is not taken forward to improving the labelled indications. Reporting requirements for medicinal products which use does not deviate from standard practice should be limited to SUSAR reporting.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
2 part 8	**26**	'Auxiliary medicinal product': a medicinal product used in the context of a clinical trial, but not as an investigational medicinal product;	

		Justification	
		The definition of an auxiliary medicinal product would be more appropriate for medicinal products used as a reference in a clinical trial if their use falls within normal clinical practice. Reporting requirements for auxiliary medicinal product should be limited to SUSAR reporting even if used outside their marketing authorisation.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
5 part 2b, 2d	**29**	Within six days following submission of the application dossier, the proposed reporting Member State shall 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.	**EITHER DELETE 2B AND D** Within six days following submission of the application dossier, the proposed reporting Member State shall 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.~~ **OR** **Within fourteen days following submission of the application dossier, the proposed reporting Member State shall notify the sponsor through the EU portal of the following:….**
		Justification	
		The assessment whether a trial does not fall within the scope of the Regulation (i.e., whether it is a non-interventional trial) or whether it is a low-interventional trial are both issues of a formulaic nature. They require the judgment of specialists familiar with the type of clinical situation in question. The assessment cannot be part of a purely formulaic process and will therefore require a longer timeline.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
6 part 4	**31**	The reporting Member State shall submit Part I of the assessment report, including its conclusion, to the sponsor and to the other Member States concerned within the following time periods: (a) within 10 days from the validation date for low-	The reporting Member State shall submit Part I of the assessment report, including its conclusion, to the sponsor and to the other Member States concerned within the following time periods: (a) within **21** days from the validation date for low-intervention clinical trials;

		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.	(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.
		Justification	
		We appreciate the Commission's aim to shorten the approval timelines for the approval of clinical trials. However, we do feel the suggested timelines are very tight and may cause problems for both the Regulatory Authorities and for the Sponsors to consider proposals fully. We therefore propose a longer period of assessment for the low-intervention clinical trial category.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
6 part 5	**30**	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.	**No specific suggestion, because major addendum required**.
		Justification	
		There is no description as to how the reporting Member State and the concerned Member States shall reach an agreement in case of major differences. We suggest that a formal procedure should be established outlining the minimum steps that should be undertaken to reach agreement	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
7 part 2 and part 3	**32**	2. Each Member State concerned shall complete its assessment within ten days from the validation date. It may request, with justified reasons, additional explanations from the sponsor regarding the aspects referred to in paragraph 1 only within that time period. 3. For the purpose of obtaining additional explanations from	2. Each Member State concerned shall complete its assessment within **fourteen** days from the validation date. It may request, with justified reasons, additional explanations from the sponsor regarding the aspects referred to in paragraph 1 only within that time period. 3. For the purpose of obtaining additional explanations from the

		the sponsor, the Member State concerned may suspend the period referred to in paragraph 2 for a maximum of ten days.	sponsor, the Member State concerned may suspend the period referred to in paragraph 2 for a maximum of **thirty-five** days.
		Justification	
		We propose more realistic timelines for completion of the assessments based on the analysis of over 1000 studies handled by the Ethics Committee of the Medical University of Vienna in the year 2011. The interaction between Ethics Committee and sponsor (irrespective whether it was an academic or commercial study) to resolve open issues (in particular regarding the informed consent) took a median of 45 calendar days. We appreciate the European Commission's aim to minimise delays in the approval process but suggest the revised timelines are more likely to be achieved. Whilst our proposed revised timelines are expressed in calendar days, these take into account that they include weekend non-working days.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
8 part 1	**32**	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.	**No specific suggestion, because major addendum required**.
		Justification	
		Our comment applies to this Article but also throughout the CTR. We could identify no instructions as to what happens if a clinical trial is authorised subject to conditions. There seems to be no mechanism provided to monitor whether or not following the approval, the conditions are subsequently fulfilled.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
9 part 1-3	**34**	*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, as well as free of any other undue influence. 2. Member States shall ensure that the assessment is done jointly by a reasonable number of persons who collectively	*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, as well as free of any other undue influence. 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.

		have the necessary qualifications and experience. 3. 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.	3. 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. An independent Ethics Committee as referred to in the Declaration of Helsinki and ICH-GCPshall be involved in the assessment of each clinical trial.
		Justification	
		The Regulation mentions Ethics Committees only in its introductory part on page 5. We are aware that the lack of inclusion of more Articles relating to the Ethics Committees activities has led to misunderstandings and in some cases hostile reactions on the part of many Ethics Committees. We support the proposal to include more information regarding Ethics Committees activities in a Recital, but also propose the addition of a clear statement relating the need to involve an Ethics Committee in the final approval of a clinical trial.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
9 part 3	**34**	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.	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 a well-experienced, knowledgeable patient/ patient representative (s) shall be taken into account
		Justification	
		We agree that the views of patients and /or their representatives (i.e. parents) should be considered in the assessments; however to legislate 'one patient' without further qualification of this involvement, does not give justice to their potential valuable contribution. We propose that a panel of patient or patient representatives who are appropriately mentored would provide a more appropriate and balanced input, than a single individual. The model used by the European Medicines Agency on patient input should be explored.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
25 part 4	**44**	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	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 implementation of this Regulation, in accordance with the EU Clinical Trials Directive.**

		Justification	
		The Article does not take into account the fact that trials contributing to the application data will pre-date the new Regulation	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
31 part 1	**47**	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 representative has been obtained, whereby consent shall represent the minor's presumed will;	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 representative has been obtained, whereby consent shall represent the minor's presumed will under the condition that **the disease of the minor is not to be classified under emergency situations (refer to Article 32)**
		Justification	
		Also parents (and guardians) are unable to give a duly consent under the enormous pressure and burden when facing a life threatening disease in their children. We are committed to ensuring that informed consent is obtained for the participation in a clinical trial. For minors, the legal representatives (usually the parents) are acting in the best interest of their child. However, when the disease is life-threatening, as in paediatric oncology, the certainty of fully-informed consent is difficult to assess. We therefore proposed that this circumstance should be considered in the same terms as recruitment to clinical trials in emergency situations (see below for further discussion of this point).	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
32 part 1	**47**	By way of derogation from points (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 may be obtained after the start of the clinical trial to continue the clinical trial and information on the clinical trial may be given 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, it is impossible to obtain prior informed consent from the subject and it is impossible to supply prior information to the subject;	By way of derogation from points (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 may be obtained after the start of the clinical trial to continue the clinical trial and information on the clinical trial may be given 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, it is impossible to obtain prior informed consent from the subject **or its legal representative (parent or guardian)** and it is impossible to supply prior information to the subject **or its legal representative (parent or guardian).**

		(b) no legal representative is available; (c) the subject has not previously expressed objections known to the investigator; (d) the research relates directly to a medical condition which causes the impossibility to obtain prior informed consent and to supply prior information; (e) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject.	(b) no legal representative is available or **in case of a minor, the legal representative (parents or guardians) cannot be expected to duly consent immediately in view of the underlying life threatening medical condition** (c) the subject or **legal representative** has not previously expressed objections known to the investigator; (d) the research relates directly to a medical condition which causes the impossibility to obtain prior informed consent and to supply prior information; (e) the clinical trial poses only a **proportionate ~~minimal~~ risk** with reference of the underlying medical condition (life threatening disease) , and imposes only **a proportionate ~~minimal~~ burden** on, the subject.
		Justification	
		In paediatric oncology a number of diseases present as a medical emergency and minors need to be entered on the relevant trial within a very short time frame (within 24 hours). It appears unethical to enforce a full informed consent procedure, as current IC documents vary between 30 to 50 pages and it is impossible to read and understand such a volume of technical/ medical information under extreme psychological stress and pressure. We strongly suggest to consider that even parents are unable to give a duly informed consent facing a dramatic cancer diagnosis where according to common experience up to 3 weeks post-diagnosis are needed to fully anticipate the new situation. Hence these situations should be acknowledged and referred to in Article 32 and hence should be considered as an equivalent to clinical trials in emergency situations. An optional two-step informed consent procedure is suggested for this type of situations when the patient should enter immediately on a clinical trial appropriate for the medical condition delivering best care involving standard practice but might also involve a scientific upfront question targeting treatment optimisation: As a first step, we propose that a short document (max. two pages) providing the key information should be signed by the legal representatives when the diagnosis of a life-threatening disease is given. Signature on step one should be given in front of testimonies who also will sign the document. Step two should involve the full informed consent information as deemed appropriate within a given clinical trial and should be obtained as soon as possible but within two to four weeks after diagnosis.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***

Explanatory memorandum 3.5	**7**	The rules on safety reporting follow the principles of the applicable international guidance documents. Compared to Directive 2001/20/EC, the rules have been streamlined, simplified and modernised as follows: • The option to exclude reporting by the investigator to the sponsor of adverse events, if this is provided for in the protocol; • Direct reporting of suspected unexpected serious adverse reactions by the sponsor to the European database EudraVigilance; • Simplified submission of the annual safety report by the sponsor. Moreover, 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 apply.	• The option to exclude reporting by the investigator to the sponsor of all **expected** adverse **events including the 'serious' category with regard to hospitalisation and prolongation of the latter,** if this is provided for in the protocol; **Simplified submission of the annual safety report** by the sponsor. Moreover, the annual safety report is not submitted for authorised investigational medicinal products that are used within their authorised indication **or if their use outside the authorised indication qualifies within a standard treatment approach in the given protocol.** For these products, the normal pharmacovigilance rules apply.
		Justification	
		It is stated that compared to Directive 2001/20/EC, the rules have been streamlined, simplified and modernised as follows HOWEVER • The option to exclude reporting by the investigator to the sponsor **of adverse events**, if this is provided for in the protocol **does not go far enough since this statement implies that all event falling under the "category serious" still need to be reported. In particular the notion of seriousness referring hospitalisation and /or prolongation of hospitalisation is too broad as both characteristics are inherent and expected side effect of many cancer drugs. This causes unnecessary reporting of standard cancer treatments.** The possibility to have a simplified submission of the annual safety report by the sponsor or no annual safety report authorised investigational medicinal products that are used within their authorised indication is welcome. HOWEVER, that implies again that there is a need for annual safety reporting on all medicinal products used outside their authorised indication (even if they are a standard treatment.) and therefore we proposed to amend the text as outlined to include in this simplified reporting also standard treatments.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
39 parts 1 & 2	**50**	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	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 authorization **and their**

		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. 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.	**use falls outside normal clinical practice**, 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. 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.
		Justification	
		The Regulation correctly identifies that no additional safety information is required if an investigational medicinal product is used in accordance with its marketing authorisation in a trial protocol. However, for trials using an investigational medicinal product off-label, the Regulation is mandating annual safety reporting regardless of whether their use is within a low-interventional trial and therefore, by definition not of any substantially greater risk to the patient than standard treatment. The substantial benefits of the low-intervention trial category clinical trials that include authorised drugs used off-label is considerably negated if the requirement for the Annual Safety Report is not equally proportionate. Whilst we appreciate the importance of robust pharmacovigilance, the safety data collected in Annual Safety Reports from products used in accordance with normal clinical practice will provide NO additional information over what is already known about the safety profile of the products and will perpetuate an enormous and unnecessary administrative burden without benefit to patients.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
41 part 1	**51**	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.	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 **unexpected** serious adverse reactions.
		Justification	
		The text in Article 41 part 1 did not make sense. A suspected serious adverse reactions would imply all reported SAEs with a possible relationship to the investigational medicinal product would need to be reported the license holder. This would be an unrealistic expectation and we wondered if there was a typographical error omitting the word ‘unexpected’	

Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
Annex III	**79**	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.	The investigator shall be responsible for reporting to the sponsor all **reportable** serious adverse events **as defined in the clinical trial protocol** 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 **defined as reportable in the clinical trial protocol** 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.
		Justification	
		In Article 37, part 2 (page 50), it states that 'The investigator shall immediately report serious adverse events to the ***sponsor unless the protocol provides, for certain adverse events, that no reporting is required'***. This needs to be reflected in the Safety Reporting guidelines in Annex III (page 79)	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
Text with EEA relevance (41)	**21**	(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	(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 or **have already a traceable history of use in standard treatments, 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

		general rules on labelling are inappropriate in view of the very controlled setting of the use of radiopharmaceuticals in clinical trials.	product, where the general rules on labelling are inappropriate in view of the very controlled setting of the use of radiopharmaceuticals in clinical trials.
		Justification	
		We argue that for investigational medicinal products that are being used according to standard practice, the risks and safety profiles are known and normal drug labelling and accountability should apply. There would be no benefit in applying additional trial labelling even if medicinal products are used outside their marketing authorisation, as this will not contribute subject safety and the reliability and robustness of data generated in such a clinical trial.	
Article	***Page***	***Text proposed by the Commission***	***Suggested Amendment***
Annex IV Part 3	**85**	ADDITIONAL LABELLING FOR AUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS 7. 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 and subject	AUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS do not require additional trial specific labelling.
		Justification	
		The additional labelling of medicinal products used in clinical trials has proved an expensive and in many circumstances unnecessary additional burden in the conduct of a trial. We strongly advocate that medicinal products that are used according the standard practice, regardless of whether this is outside the marketing authorization should have no additional labelling applied over and above normal drug traceability. Trial specific labelling should be reserved for truly experimental investigational medicinal products only.	