

COMMENTS OF THE SPANISH SOCIETY OF CLINICAL PHARMACOLOGY ON THE CONCEPT PAPER ON THE REVISION OF THE “CLINICAL TRIAL DIRECTIVE” 2001/20/EC

As a preliminary consideration, we would like to highlight the following general issues to be kept in mind:

- The procedure for submission, assessment and approval of clinical trials at the national level includes both the assessment by the National Competent Authority on medicines (NCA) and the assessment by the Research Ethics Committees (REC) . It is our view that the improvement of the clinical trials authorisation process in the EU could only be achieved if both components of the system in the new model (the REC and the NCAs) work efficiently.
- It is acknowledged that RECs are the exclusive competence of MS. Nevertheless, any proposal for a legislative change at the European level should carefully consider the possible impact on the REC component of the process at a national level and, whenever possible, should contribute to a better function of all national REC systems.
- Across Member States, the national REC systems have different organisations and different relations to the NCA on medicines. Usually, the National Authority for REC and the NCA on medicines are not the same institution.
- The separation between RECs competences and NCAs competences at the national level will heavily influence the separation between the areas to be included under the scope of an eventual Coordinated European Procedure and the areas to be kept at a pure national level. Other aspects such as the creation of a single European submission system also should bear in mind this dual system.

Consultation item no. 1: Single Submission.

The decrease in redundant evaluations and the elimination of the unnecessary administrative burden linked to clinical trials authorisation requires that changes in legislation consider both National Competent Authorities on Medicines (NCA)¹ and Research Ethics Committees (REC). However, the role and need for improvement in the REC systems and the possible impact of this proposal on RECs function are ignored in the document.

¹ Throughout the document, NCA means Medicines National Competent Authority unless otherwise specified

We are concerned about the potential negative global consequences of building a single submission system only driven by the submission to NCAs and ignoring the needs that the REC National Systems have in order to fulfil their responsibilities in a more efficient way. RECs have an essential role for the protection of patients' rights and the medicines authorities should see them as a crucial partner in the process of the clinical investigation with medicines.

Focusing on submission to NCAs, it is agreed that a single submission would be a useful tool, provided that all the necessary documentation for the application is standardised and identical among all NCAs and that all the documentation can be submitted in only one language (e.g. English). Moreover the single submission system should only be an option for multinational CTs, not for purely national ones. The added value of the single submission would be less clear if the establishing of different national requirements for some specific situations were permitted.

All information addressed to participants (e.g. information to obtain the informed consent, special instructions for participants, etc.) is needed in national languages, even in a potential single submission system. Nevertheless, these are common documents that could also be included in English, with verbatim translations then being submitted to the Ethics Committees in the Member States concerned.

The creation of a single electronic portal for submission would ensure the maximum efficiency of this approach.

However, as we have mentioned before, the proposal for a single submission also needs to preserve the facilitation of the submission to the RECs systems.

The ethical review process and the Research Ethics Committees (REC) networks are (and will be) organised at a national level. A good functioning of the whole system without duplication of activities imposes a strong need for preserving formal links between the Ethics review structure and the Competent Authority within each country. Some Member States (e.g. Spain) have organised a single entry point and a shared communication system for RECs and the NCA, that should not be placed in danger by a single European Submission System for NCAs.

There is an urgent need to improve the liaison between RECs and NCAs (e.g. an effective management of SUSARs should be established). It is important to avoid that investment in the simplification of NCA submissions, already rather similar, put at risk the investment in the improvement of the exchange of information and the understanding between the NCA and the national structure of RECs.

In summary, the concept of single submission, although attractive, brings with it the danger of worsening the whole system of clinical trials authorisation if it is only driven by the aim of improving the European coordination of National Competent Authorities (NCA) and becomes an obstacle to a better coordination between Research Ethics Committees (REC) and NCAs at the national level

Consultation item nº 2: Separate assessment

It is agreed that a separate assessment will not solve the issue. Nevertheless, divergence between assessments or lack of mutual trust is more relevant at the RECs level rather than at the NCAs level. Once again, focusing on the existence of possible independent assessments by NCAs instead of the issues related to the duplicate assessments by Ethics Committees could lead us to changes in legislation that in fact do not improve the efficiency of the whole system.

Therefore, as the REC system is the major source for duplicities and different requirements, the most effective tools to minimise divergences within the system would be the good coordination between RECs and NCAs at the national level as well as fostering the European coordination of the existing national RECs networks.

Consultation item nº 3: Single submission with central assessment

We agree with the appraisal. A central assessment is not feasible, nor efficient or convenient.

Moreover, the differences in medical management between Member States may pose difficulties for the assessment of the study design and fall within the area of ethical discussions, making it difficult to provide a fair judgment from a single centralized office

Consultation item nº 4: Single submission with a subsequent "coordinated assessment procedure". Is the above catalogue complete?

Consultation item nº 5: Do you agree to include the aspects under a), and only these aspects, in the scope of the CAP?

Clarification of the REC and NCA respective roles and responsibilities would be a step forward to improve the effectiveness of the system of reviewing and supervising clinical trials. However, the separation proposed between tasks assigned to REC and NCAs is artificial, ill-founded and unrealistic. The R/B evaluation, including the methodological issues, is an integral part of the ethical evaluation at REC. Moreover, there are other important ethical issues concerning an equitable selection of subjects, a special protection of vulnerable people, etc., which are not even mentioned, so the "catalogue" is not complete.

The areas that could be assessed by NCAs only and therefore included within the scope of an eventual Coordinated Assessment Procedure, are those related to the investigational medicinal product quality and knowledge as well as several "administrative" or legal aspects (e.g. labelling and management of the medication, aspects related to the sponsor, etc.).

The acceptability of the clinical trial in view of anticipated benefits compared to risks and inconveniences for trial subjects falls within the responsibilities of Ethics Committees as does the assessment of the intervention as compared to normal clinical practice that may differ

substantially between countries. The design of the trial includes several concepts such as methods, objectives, endpoints, inclusion and exclusion criteria, vulnerable populations, study procedures, adverse event reporting, statistical plan and quality control and there is no doubt that the differences in medical management between Member States and centres may pose difficulties for achieving a single European opinion at that level (e.g.: the acceptability of the control arm according to national medical practices).

If this is also included within the NCAs responsibility and this duality is thus maintained, the possibility of divergent opinions (CAP vs. REC) will remain. It should be possible to design a process where this assessment (benefit/risk assessment) is assessed only once and where there is a real and explicit delegation of responsibility from National Authorities to their national RECs. This will help to give the REC system an appropriate coverage of legal responsibilities and resource provision².

Finally, we agree that the aspects under sections b) and c) should remain within the **scope** of RECs at the respective Member States.

Consultation item nº 6: Disagreement with the assessment report. Which of these approaches is preferable? Please give your reasons.

If a Member State disagrees because of a “serious risk to public health or safety of the participant”, either it is a local issue (and therefore falls within the scope of RECs) or it would be hard to imagine that there is a real risk only seen by a few Member States and that cannot be resolved by consensus among all concerned Member States.

An “opt out” option by a NCA implies that a separate assessment is carried out by the concerned Member States at the national level, which is against the philosophy of the proposal. Therefore, such an “opt out” approach is only justified based on aspects related to local medical practice or other aspects that are under the specific responsibilities of the ethics committees.

In case the coordinated assessment only deals with aspects that are responsibility of NCAs and are not subject to REC assessment (e.g. quality of the product), a consensus should be always achieved and the opt-out option should not be accepted

Neither the voting nor the referral to the Commission or the Agency are legitimate options to rule out a local concern in a Member State as expressed by a national REC.

² In order to fulfil their responsibilities before their citizens, a Member State could assign different tasks to different National Authorities (NCAs on medicines, National authority on Ethics Committees) who could also then make different delegations of responsibilities to the national REC system.

Consultation item nº 7: Mandatory/optional use. Which of these three approaches is preferable? Please give your reasons.

Based on the objective of simplification of procedures and better use of resources, we believe that a mandatory system for all trials, including those that are exclusively national, is an inappropriate approach. An optional system for all trials is also inappropriate for the same reasons.

A mandatory system for all multinational trials is attractive, although it is mandatory to reinforce the existing voluntary harmonisation procedure and ensure its efficiency and resource provision in order to avoid uncertainties about its correct functioning.

Consultation item nº 8: Tacit approval and timelines. Do you think such pre-assessment is workable in practice? Please comment.

A pre-assessment leading to a classification of trials according to risk (with consequent differences on the authorization procedures) is positive and workable but there are several considerations to be made:

- To assess the risks of clinical trials in order to propose a risk-adapted legislation in relation to the intervention by the NCAs, it would be necessary first to clarify the difference between the risks related to the medicinal product in question and the risks inherent to the interventions (e.g. diagnostic procedures) due to the trial. It is the REC responsibility to assess the risks and inconveniences of the trial procedures as they do with the rest of investigations not involving medicines (clinical investigations with medical devices, surgery, etc.). It is questionable that the risks of the trial procedures could justify a different review by the National Competent Authority on medicines, which should be concerned with the risks associated with the product.
- In order to propose a risk adapted NCA intervention, it would be preferable to define 3 clear cut categories of CTs according to the previous assessment and approval of the use of the medicinal product by the NCAs: 1) Type A, those using marketed medicinal products under the authorised conditions or being part of standard treatment in a Member State concerned; 2) Type B, those using authorised medicines in a different way than approved; and 3) Type C, non-authorised medicines.
- With this proposed classification, Type A CTs would not need authorisation by NCAs, a register by NCA and ethical review by REC would suffice. Type B CTs would require authorisation by the NCA but with a lighter or abridged procedure.
- In any case, it should be addressed as a self classification by the Sponsor, leaving open the option of switching the trial to a higher degree of risk whenever the NCA disagrees with the self classification proposed by the sponsor.

- Of course, there are other dimensions of risk that are not related to the product itself and that could increase the risk in a type A clinical trial (e.g. risks derived from invasive diagnostic procedures). This will be dealt by the REC in their assessment.
- See below a table summarising the proposed classification of trials, based on the medicinal product, in order to allow a risk-adapted NCA intervention

Category	Type of CT based on Medicinal product previous assessment and authorization by NCA	NCA intervention	REC review
A	Phase IV CTs using medicinal products under the authorised conditions of use	Notification and register only	Yes
B	CTs with authorised products used in different conditions (new indications, new population, new posology,).	Authorisation with abridged procedure	Yes
C	Phase I to III CTs, or trials with non-authorised products in the member state	Full review and authorisation	Yes

Consultation item nº 9: Limiting the scope of the Clinical Trials Directive. Harmonised and proportionate requirements for all clinical trials under the scope of the present CT Directive. Do you agree with this appraisal. Please comment

There is a clear need to change the current definition of “non-interventional trial” which has proven to be too rigid and restrictive, thus leading to strong inconsistencies across EU countries and different stakeholders within each Member States, as well as unnecessary administrative burden of intervention. At present, there are studies that do not deserve the intervention foreseen for clinical trials but, at the same time, do not entirely comply with the conditions established for non-interventional trials. Sometimes those studies are considered clinical trials and this causes unnecessary and distorted requirements in relation to financial resources, insurances, provision of medication, etc.

We propose modifying the definition of a non interventional study in order to include all non interventional studies according to the epidemiology point of view. Following the DSUR and WHO definition of an interventional clinical trial, the definition of a non-interventional study would be the opposite concept, which focuses exclusively on the second condition of the current definition: “the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study”.

The fact that in practice the authorized medicine is not used in full accordance with the terms of the marketing authorization or that the study implies the use of additional diagnostic or monitoring procedures in the patients being followed up are not reasons to switch the classification of “ non interventional study” to a “clinical trial”. The key factor for the definition of non-intervention is, as mentioned before, the intentional assignment of a patient to a specific intervention, which in essence means either the use of a non-authorized medicine or the existence of randomisation.

Requirements for the Ethics Research Committees approval of the study and the informed consent or even requirements for GCP compliance in non interventional studies could be established in a specific manner through particular European guidance’s for non interventional studies. These guarantees should be achieved by other means than distorting definitions. Including studies designed as epidemiological studies into the definition of clinical trials because of additional follow up procedures imposes unnecessary (and often unsolvable) complications such as those related to medicines labelling and supply.

On the other hand, requirements applicable to phase IV randomised clinical trials should be strongly simplified in the new CT directive as they should be closer to those of non interventional studies. Clinical trials on medicines used under their authorized conditions could be waived from NCA authorization and be only subject to register and REC ethical review.

Consultation item nº 10: Excluding clinical trials by ‘academic/non-commercial sponsors’ From the scope of the Clinical Trials Directive. Do you agree with this appraisal? Please comment

We agree with the appraisal. The final objective of the directive is that of ensuring appropriate patient safety and a reasonable benefit/risk of their participation in clinical trials. To that respect the safety of patients can be equally threatened or ensured by commercial and non-commercial sponsorship, and the key aspects of assessment should be shared by both types of trials. Nevertheless, we must admit that the administrative burden is deterrent for independent researchers. As most clinical trials performed by independent researchers are those of type A (authorized medicines), a solution can be found through changes in the directive as those proposed before for type A trials: administrative approval not required, only REC evaluation needed, reporting of SUSARs done directly to pharmacovigilance services, etc.

Consultation item nº 11: More precise and risk-adapted rules for the content of the application dossier and for safety reporting. Do you agree with this appraisal? Please comment

We fully support the idea of a risk based adapted rules. For this purpose, a few risk categories need to be defined and, as we have mentioned before, the authorization status of the medicinal product appears as the most adequate factor to define those categories

Other dimensions of risk, such as the risk of the trial subject as compared to normal practice, are subject to a more trial specific assessment by the REC and may constitute an inadequate

factor to assign different European rules, as categorization is not under the remit of NCAs and lacks homogeneity across RECs.

We propose the following specific risk-adapted rules:

- Waiver from the periodic trial safety report obligation for type A trials (marketed medicines). This is redundant with the periodic safety report of the medicine that is already being submitted to NCAs by the Marketing Authorization Holder (MAH). For cases where the sponsor does not coincide with the MAH (independent studies), it will be enough to ensure that the sponsor gives access to the safety information of the study.
- For type A trials, information on the investigational medicinal product should be limited to the approved Summary of Product Characteristics (SPC).
- For type B trials, information on the IMP should be the SPC plus the necessary information related to the new use of the product (new doses, new populations, etc.)

Consultation item nº 12: Are there other key aspects on which more detailed rules are needed?

The following detailed rules related to the medicinal product are also proposed:

1. Adaptation of art. 19 of Directive. Instead of “Unless Member States have established precise conditions for exceptional circumstances, investigational medicinal products and, as the case may be, the devices used for their administration shall be made available ***free of charge by the sponsor***” it would be better to establish that “Unless Member States have established precise conditions for exceptional circumstances, investigational medicinal products and, as the case may be, the devices used for their administration shall be made available ***free of charge for the clinical trial participants.***”

Explanation: The provision of the IMP free of charge by the sponsor should not be a general rule and may constitute a problem for trials with marketed medicines.

2. Exemptions for specific trial labelling are needed in the cases of investigational medicinal products with a marketing authorization in the concerned MS. In these cases, traceability of medicinal products to be used in the clinical trial could be ensured with alternative measures, such as recording of the prescription details (including batch number) in the case report forms or having records of the dispatch by the Pharmacy Service to the investigator.

3. Adapted GMP requirements are needed for investigational medicinal products in cases they are prepared in hospital pharmacy services according to accepted standards.

Consultation item nº 13: Clarifying the definition of IMP and establishing rules for “auxiliary medicinal products”. Do you agree with this appraisal? Please comment.

We agree. The term IMP should be restricted only to those products that are investigational in a clinical trial either as a test drug or as a reference product (active or placebo). The rest of medicinal products used in the context of the clinical trial (background therapy, rescue therapy, etc.) should be considered as non-investigational medicinal products and not be subject to disproportionate requirements although they should be carefully recorded and taken into account for the evaluation of efficacy and safety results

Consultation item nº 14: Insurance/indemnisation. Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

As a starting point, it is our opinion that details on the insurance provisions should not be developed in a European directive. Only very general and basic principles could be addressed at that level.

Once again, the main issue would be the classification of clinical trials according to risk for patients. For insurance/indemnisation purposes, the previously proposed classification in 3 categories based on the medicinal product authorisation status, may not be fully appropriate as it does not cover all risk dimensions of the trial. A type A trial with a marketed medicine could have extra-risks related to diagnostic procedures, organizational issues, confidentiality concerns, etc.

It is the REC responsibility to assess the risk for participants in each trial and the measures taken to properly manage the risk. It could be workable to further categorise the trials in a similar way to that proposed in the EU document “Ethical considerations for clinical trials on medicinal products conducted with the pediatric population” : 1) No additional risk with respect to normal clinical practice or minimal risk; 2) Minor increase of risk over normal clinical practice; 3) Greater than minor increase of risk over normal clinical practice. It would be necessary to define “Minimal risk” and it is suggested to adopt the original US definition and now globally accepted: “Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests” (45 CFR 46.102(h)(i)).

For those type A trials with no additional risk with respect to normal practice, no specific provisions regarding insurance or insurance/indemnisation should be foreseen. The standard medical practice provisions should apply. For the rest of trials, specific provisions for indemnisation could be considered.

Some examples are summarised in the table below.

Type of CT	Type of Risk	Examples (may be others)	Specific provisions
A	No additional risk over the one of clinical practice (minimal risk)	Phase IV CTs using medicinal products under the authorised conditions of use and no invasive evaluation proposed.	No need for specific insurance
A, B	Minor increase of risk over normal clinical practice (to be assessed by REC)	Phase IV trials with invasive procedures or some trials with authorised products but in new populations	Specific provisions needed. Mandatory specific insurance possibly inappropriate
C	Greater than minor increase of risk over normal clinical practice (to be assessed by REC)	Phase I to III CTs	Specific provisions needed, either insurance or specific indemnisation provision

With regards to the possibility of removing insurance requirements for some low risk clinical trials it is important to remind that this does not mean that the liability of the investigator or sponsor is removed. Spanish regulation already considers the possibility of insurance waiver for low risk clinical trials but do not remove the liability of the investigator and/or sponsor. The patient should have the right for insurance/indemnisation in the unlikely case that a trial subject suffers an injury.

The insurance/indemnisation by Member State could be a viable solution for clinical trials by academic/non-commercial sponsors because insurance/indemnisation requirements and their additional costs are a significant barrier to research.

Consultation item nº 15: Single sponsor. Do you agree with this appraisal? Please comment.

The option of multiple/joint/shared sponsorship should be discussed to find an option that fits with the needs of the non-commercial trials run by cooperative investigation groups.

Consultation item nº 16: Emergency clinical trial. Do you agree with this appraisal? Please comment.

It is agreed. The possibility to start the investigation without patient consent should be foreseen in the trial protocol and this possibility have been evaluated properly by the Ethics Committee, as it is established in the Helsinki Declaration.

This is the procedure established in the current Spanish law since 2003 and it has worked satisfactorily.

Consultation item nº 17: Ensuring compliance with GCP in CT performed in third countries. Do you agree with this appraisal? Please comment.

We agree with the appraisal.

The requirement of registration within the EudraCT database for trials not conducted in any EU country might be waived if the study had been registered in any of a limited number of public databases complying with the World Health Organization International Standards for Clinical Trial Registries

Consultation item nº 18: Figures and data.

No further comments.