EU Commission position paper /Changes on EU Directive 2011/20/EC

Name : ACRP

Item	TOPIC	COMMENT
1	**Single Submission to EU Portal**	A single submission could reduce administrative work and time. However, it will only occur if all European Countries harmonized their requirements in advance.
2	**Assessment by MS**	We believe a single assessment and authorisation for all countries of the Protocol and Investigational Product dossier is sufficient. However, the current system has the merit of stimulating a competition in terms of speed and efficiency between MS, which allows MS to differentiate themselves in order to be more attractive (should they wish) for the conduct of clinical research. The challenges will remain also in case of CAP, since different outcomes may be required across MSs. However, in case of a large study submission document this would need to be harmonized across different countries, a single submission would reduce the administrative work. MSs would have to agree to agree or each MS would provide feedback to the EU and a final 'response' be given to the sponsor.
3	**Assessment Centralized**	Overall, most elements of the dossier review could/should be centralised: - With respect to the IP dossier we believe a central review is efficient and cost effective in principle, even if only a few countries participate in each clinical trial. Cost and speed should differentiate EU attractiveness as compared to USA and emerging countries. - The Ethical review of the scientific aspects of the protocol and its components could be centralised for all MS in a central Ethics Committee with individual representatives from all MS. Translations into local language of documents destined for patients requires local review, and the MS representative should have a system to review the suitability of the proposed investigational sites and investigators for the conduct of the clinical trial. - The EU could invest in a Committee structure that is of course excellent in scientific skills, and also extremely aware that the EU is competing with the other regions of the world in terms of speed and added value. Requests for modifications to the submitted dossier should be relevant and support enhanced Ethical conduct or an improved development of the IP rather than demonstrate knowledge of the reviewers. Costs for this Committee should be born at EU level, as attracting clinical research is crucial for innovation regardless of its source, and we compete with other regions in the world based on cost and speed (as quality is generally monitored very closely everywhere in the world). The possible unintended consequence of differentiation between academic researchers and commercial sponsors would be that new legal structures will be created that blurr the distinction between the two types of entity in order to reduce costs. - The EU should take care to protect the intellectual property of the sponsors and researchers by investing in a state of the art IT infrastructure, with severe legal consequences for breaches by those who have access. Centralising the submission would hopefully also mean that the required investment for this type of infrastructure would be maintained at all times. - One option that could be considered in order to foster continuous improvement would be to allow choice to sponsors: between a central, unique review by a highly efficient Committee representative of all MS; or an application in the same way as it is done today. Member States would then have the option to improve on the Centralised system or not. However, we must take into consideration that most clinical trials are being done is small numbers of MSs due to the high administrative workload. There must also be a reliable structure without time delays.
4,5	**Coordinated Assessment Procedure**	- The CAP review may wish to also consider the environmental impact of the Investigational Medicinal Product. - The CAP review should consider general aspects of investigator suitability defined in the protocol: which core competencies should the investigator have. The assessment of these core skills should be recognised at a EU level (eg: a EU recognised Medical Doctor or Dentist degree, a EU recognised GCP certification). Patients participate in clinical trials across borders in the EU. -Please clarify item b) ethical aspects related to informed consent, recruitment and . The term 'reward' may be construed differently than the intent of this section. Do we reward 'investigators' for enrolling subjects? Do we reward physicians for referring patients for potential trial participation? If this section is to notate the potential unethical or conflict of interest view of these activities - then we concur. However, if this section is to outline that 'this is permissible', then we do not concur. - RECOMMENDATION: Delete the word reward from this section, and state compensate for participation in the clinical trial (liz wool) (c) include also for item (a) the following: suitability of study staff by clinical - medical licenses/certifications to perform their delegated responsibiltiies (c) include also for item (a): training of investigator and study staff - GCP, protocol, therapeutic area, delegated study responsibilities, and documenation of training.

6	**Disagreement with the Assessment Report**	There is a definite need for further clarification on the three given options as all three options are challenging. The Opt -out is the simplest resolution option. However, it must be communicated to all relevant countries and should only be implemented if transparency on the decision is available. Sponsor would need to be notified quickly if a MS "opted-out". Considering CAP Procedure, we see no improvement in CTA Submission and approval. Opt Out is preferable since clinical trials are national in terms of responsibility . Majority vote is a risk as strong members could become more influential. Feedback and simple majority vote would result in a more functional single EU submission. However, communication and compliance would have to be ensured. The Referral to the Commission EU agency is the preferred option when it may provide robust review. This option could result in a time delay. MS who disagree with the CAP approval of a clinical trial should have the option to opt out, at all times as specified. Local MS assessment of safety for participants must prevail. MS who disagree with the CAP non-approvability of a clinical trial should have the option to have a separate local MS review subsequent to or in parallel of the CAP process. This separate process should not result in additional cost or delay for the sponsor. Rationale for this option: some MS may develop specific competencies or infrastructure that would allow conduct of particular research in their MS which would not be suitable in other MS. This approach would foster innovation and continuous improvement through competition. The MS approval of a non-approved by CAP clinical trial should be validated by a specialised Committee for scientific / Ethical appeal at EU level within maximum 30 days; the grounds for approval of this process should be the additional differentiating features presented by the MS and not a different view of the clinical trial per se.
7	**CAP Mandatory/Optional for Trials**	CAP should be optional: however when a CAP approval is granted for a clinical trial (for the defined aspects under 1.3.1), it is valid in all MS and should not need to be repeated in individual MS. It seems that if trial is conducted in only one MS that MS should have oversight. If more than one MS than single submission would apply.Cost and speed of review should be competitive with other regions in the world. CAP review should be more attractive to sponsors, and therefore the preferred option, rather than imposed and therefore stiffling continuous improvement. Note that this option is relevant for multinational studies. For CAP procedure, the national trials does not add any benefit, unless there is significant investment by the EU to make it attractive.
8	**Tacit Approval and Timelines**	Pre-assessment should be a decision of the committee board that completes the CAP assessment in order to assign correct levels of internal CAP process resources. The interest of the sponsor is the outcome of the CAP process, with a simple, cost -effective and fast process. A pre-assessment could be part of an internal procedure but should not delay the overall response time required by the EMA, much like the process used by the Canada Health Autorities.
9,10	**Scope of Directive**	Agree with appraisals. Same standards should be implemented during development and for marketed products.
11,12	**Risk Driven Requirements**	There is a need for clarification for the IMP. The IMP may impact the safety profile of the pharmaceutical product used in specific indication. Other key aspects to develop: a Tolerability of Risk framework. This framework would allow a robust assessment of risks of treatments based on evidence that is consistent accross therapeutic indications and adverse reactions. It would define tolerable levels of adverse reaction we accept in the EU depending on the degree of severity of disease and possible current levels of adverse reaction in standard of care. It would foster transparency in risk taking and timely decision making in line with evidence rather than heuristic bias, and thus significantly reduce costs. It would also consistently address concerns raised by the public as the framework could be adapted to MS sensitivities.
13	**Definition of IMP/non-IMP**	It is important to differentiate between IMP'S and Non IMP's and concomitant medications used with regards to safety requirements. Clarification will allow consistency in approach.
14	**Insurance Requirements for Low Risk Trials**	Both options are possible. By clearly defining low risk trials, insurance requirements could be removed. Since issue is 'local oversight' - MS should be responsible for coverage and damages. As clinical trials can also be an option of treatment for patients, it would be preferred that clinical trial insurance coverage is mandated in the MS national legal system and not a separate insurance. Liability agreements between sponsor and investigator could then differentiate which liability would be incurred by the sponsor for possible negligence. Another option could be a EU fund which is used for specific risks.
15	**Single Sponsor**	Option #1 should remain as it is preferable to have one single entity responsibe without relaying on national rules. Ultimately, one point of contact and only one 'final decision' must be obtained. However, this single entity should be able to share the risks according to contractual agreements it has itself with other parties.
16	**Emergency Clinical Trials**	Fully agree to bring the EU directive in line with internationally - agreed texts for emergency clinical trials.
17	**Ensuring GCP Compliance**	Increased transparency and registeration in the EU clinical trials database EudraCT and published via the public EU-database EudraPharm would help as it could also result in increasing quality level of these studies. However compliance can only be ensured with on-going oversight of implementation process which is not discussed in the preliminary appraisal.
18	**Figures and Data**	No comment with the exception to, as noted, figures and data must be quality checked for consistancy and accuracy.
19	**General Comments**	It is imperative that the directive deals with Harmonization among MSs and not the other way around. Harmonization must occur before implementation of the directive.