GILEAD
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Response to Public Consultation Paper

Assessment of the Functioning of the Clinical Trials Directive 2001/20/EC

Consultation item n°1: Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of Clinical Trials Directive?

Gilead recognizes that the Directive has resulted in improved protection for clinical trials subjects. For example, the Directive standardised the conduct of clinical trials on minors or incapacitated adults not able to give informed legal consent.

Gilead is not aware of any studies or data which shows benefits of the Clinical Trials Directive.

Consultation item n°2: Is this an accurate description of the situation? What is your appraisal of the situation?

Gilead agrees that the description is accurate; unfortunately the processes and requirements vary greatly between National Competent Authorities (NCAs). The requirements of some individual NCAs go beyond those specified in the Directive and in addition, timelines for authorisation differ between NCAs (eg, 10 days for validation + 60 days for authorisation vs. a total of 60 days).

Another common issue is the difference of opinions among NCAs; for example protocol amendments requested by one NCA will often be unacceptable to other NCAs, resulting in sponsors being required to manage country specific amendments which can become costly and time consuming.

Consultation item n°3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

Gilead agrees that the description is accurate; country selection should be based on patient population availability and not on NCA approval process and timelines. Due to divergent opinions and timelines in different Member States, Industry may not select a specific country in order to not delay the development of a compound, thus possibly depriving potential subjects from that specific country.

Gilead Sciences International Limited Flowers Building Granta Park Abington Cambridge CB21 6GT
Tel +44 (0)1223 897300 Fax +44 (0)1223 897282
Registered in England No 3177490

Consultation item n°4: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

Option 3.3.1, Reliance on voluntary cooperation of NCAs, will continue to lead to confusion as Member States may opt in or out during the review of a particular study. Another point to consider is that as this process is a voluntary initiative, NCAs may decide to not participate in the process at all.

Option 3.3.2, Community-wide streamlining of NCA-authorisation process for clinical trials is our preferred choice as it would provide industry with a consistent process with agreed timelines. This option would ensure that an application can be submitted just once to the selected competent authority and that study start-up can commence in the entire EU without any additional delays.

Gilead believes the following should also be considered:

§ The use of a submission gateway (potentially to the EMEA) where the selected competent authority has immediate access to submission packages.
§ Community-wide streamlining of NCA-authorisations should only be used when applying for a multiple member state submissions. Single State Submissions should be submitted through the same process, but should be evaluated by the member state concerned.

Consultation item n°5: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

Option 3.4.1., One-stop shop for submission of assessment dossier is our preferred choice, as it would provide Industry with a consistent process with agreed timelines. This option would ensure that an application can be submitted just once and that study start up can commence in the entire EU without any additional delays.

Gilead believes the following should also be considered:

§ The pros and cons of a decrease of regional review of clinical trials
§ The implications to regional job availability and funding for EC's organizations.

Consultation item n°6: Is this an accurate description of the situation? Can you give other examples?

Gilead agrees that the description is accurate and that there is a lack of clarity in regards to reporting. In order to be transparent with NCAs, industry takes a conservative approach and submits all information that might be considered significant at any level. It is difficult to tailor a submission package to each and every NCA, therefore some NCAs might receive more information than their national legislative requirements.

Gilead agrees that the divergence with SUSAR reporting expectations is frustrating and cumbersome – Industry would prefer to route all reports to Eudravigilance and the NCAs access reports they require from there – even if it required submission of all SADRs vs SUSARs. Some companies are reporting all SADRs to EVCTM which may also explain the increase in reports as they are choosing to over-report rather than build complex processes to meet divergent requirements.

Scope of trials is generally clear but a grey area is those sponsored studies by academic institutions which are reported to the MAH for pharmacovigilance – neither volume 9a or the Clinical Trials Directive adequately address the reporting expectations of an MAH or company with active trials who have such data received and feel they have expedited reporting obligations, specifically if data comes from outside the EEA. A Company does not always know a report has been sent to EVCTM or EVPM; many conservatively report – again adding to the increase in reports seen by NCAs.

Another example regarding the inconsistent implementation of the Directive is the submission of Investigator's Brochure.

Consultation item n°7: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

In terms of weaknesses highlighted in Section 4.2, Gilead feels it is misleading to suggest expedition if multiple SUSARs impact patient protection as trial sponsors also complete and prepare Annual Safety Reports of aggregate data – the issue is that the company rarely, if ever, gets feedback on such reports. Six-monthly line listings and ASRs enable aggregate overview of safety data – an individual SUSAR rarely leads to risk/benefit changes.

Increased costs are associated with all the additional safety reports required per the Directive and their submission to authorities, ethics committees and investigators. Consultation 7 will only make it better if it is agreed as a Regulation as suggested with no national variance acceptable but also if the agreed standard is reasonable and not the most conservative per current guidance's – at EU and at national level.

Consultation item n°8: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case by case basis?

Gilead has no specific comments on this item.

Consultation item n°9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

Gilead is not able to provide an example of insufficient risk-differentiation.

Consultation item n°10: Do you agree with this description? Can you give other examples?

In regards to the requirements of a single sponsor, Gilead agrees with the description. At times industry members may partner each other or with non-commercial sponsors and it is difficult to manage these partnerships when a single sponsor for each clinical trial is required.

Consultation item n°11: Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address this problem?

Gilead believes that more comprehensive guidelines will suffice in order to provide better guidance to sponsors, especially to non-commercial/academic sponsors. In order to optimise the harmonisation, existing legislations should be reviewed for consistency.

Consultation item n°12: In what areas would an amendment of the Clinical Trials Directive be required in order to address the issue? If this was addressed, can the impacts be described and quantified?

Gilead agrees that the Directive should be revised; however the optimal way forward is for it to be made into a Regulation, which becomes immediately enforceable as law in all member states simultaneously, as currently being proposed by the Commission.

Consultation item n°13: Would you agree to this option and if so what would be the impact?

Gilead disagrees with the approach of excluding "academic" sponsors from the rules of the Directive, as it should provide a consistent way of managing all clinical trials.

Consultation item n°14: In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

Gilead believes that the recently introduced legislation has outlined the needs and addressed the safety of the clinical trials subjects.

Consultation item n°15: Should this issue be addressed? What ways have been found in order to reconcile patient's rights and the peculiarities of emergency clinical trials? Which approach is favourable in view of past experiences?

Gilead agrees that the issue of emergency research should be addressed.

A verbal assent followed by a full consent by family or the patient himself (once the patient is stable) should be taken into consideration.

Consultation item n°16: Please comment? Do you have additional information, including quantitative information and data?

Gilead acknowledges the concerns raised by the Commission, however many sponsors have very robust compliance and monitoring processes in place in order to assure all sites in third countries perform to company standards.

When conducting clinical trials in third countries, Gilead expects the same standards as those adopted in the EU.

Consultation item n°17: What other options could be considered, taking into account the legal and practical limitations?

Gilead believes that the strengthening of international cooperation in GCP inspection and mutual recognition of GCP rules as described in 7.3.3 would be the optimal course of action.

Consultation item n°18: What other aspect would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments? Are SME aspects already fully taken into account?

Data protection guidelines for clinical trials should be consistent among NCAs. A more robust guidance linking the Clinical Trials Directive with Directive 95/46/EC should be taken into consideration.