Response to Public Consultation Paper

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

General comments

Since the widespread adoption of ICH-GCP from 1996 onwards, better monitoring and effective quality systems, including audits and inspections, and underpinned by the legislative framework provided by the Directive have resulted in fraud and misconduct of any type in clinical trials decreasing significantly. The reliability and value of trial results, generated with the EU, is commensurately better in 2009.

However, in some areas ambiguity and confusion persist. Working within the confines of a legislative framework has made many stakeholders more conservative and less willing/able to negotiate resolutions to their per-study problems.

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

We agree that the Directive has resulted in improved protection for clinical trial participants, but the degree of improvement varies for different types of trial sponsor.

The Directive has been particularly positive for non-commercial trials. Our members working in this sector report significant investment to ensure fulfilment of sponsor responsibilities. This has resulted in improvements in standard of conduct, protection or participants and robustness of resulting data.

We also highlight the improvement in protection due to the requirement for annual updates to the Investigator Brochure, which was previously updated on a rather *ad hoc* basis by some organisations.

However, in the UK, procedures for ethics and regulatory authorisation had already been greatly improved before the Directive was enacted into law. In this respect, the improvement in real protection for participants in industry-sponsored studies might be marginal, although costs have clearly increased as a consequence.

2: Is this an accurate description of the situation? What is your appraisal of the situation?

The experiences of our members suggest that this description is accurate, with processes and interpretations varying between NCAs. Information requirements also very between NCAs, some of which have maintained previous requirements in addition to those specified in the Directive.

However, in our experience, divergent decisions are more frequent between ECs than between NCAs. Compliance with timelines is also an issue for ECs; one contributor reports that an EC took eight months to reject a protocol amendment that had been accepted in several other Member States.

Differing processes, requirements, interpretations and decisions must be dealt with individually, increasing costs and delaying study start-up, all of which risk decreasing the likelihood of EU inclusion in future studies.

Other areas of divergence, beyond the current scope of the Directive, include contractual arrangements between study teams.

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

This description is broadly accurate.

It should be noted that the delay to "first patient in" is limited to the individual country rather than the entire EU; however, this delay could be sufficient for the study to have met its global recruitment target without sites in that country being involved. An important exception to this, though, is when a sponsor seeks authorisation in one Member State to support applications in others.

One contributor cites numerous examples applications rejected on grounds that could easily have been remedied with a brief conversation. The rejections were valid, but neither the protection of participants nor the validity of the data was at risk.

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?

NCA approval is not usually the rate-limiting step, except as a prerequisite for another layer of approval in principle (eg, EC, investigational site contract etc.). Handling all approval processes in parallel would have more impact than streamlining NCA approvals.

Voluntary cooperation between NCAs has its attractions, as this is presumably quicker and cheaper to implement than any other solution. However, a concern would be the potential for states to opt in or out in particular circumstances, or even for particular studies, leading to confusion, delays etc.

It would certainly seem excessive to take a centralised approach to trials intended to run in a single country; it may be most cost/time-effective to use a centralised approach for trials intended to be run in a minimum of three Member States. However, Member States would seem unlikely to give up control of approval entirely, so an exclusively centralised procedure seems impractical.

The appointment of a member state to act on behalf of others, which retain some degree of input, seems more realistic.

However, Member States will have to be far more willing to amend associated (sometimes non-clinical trial) legislation if a more harmonised procedure is to be feasible. Examples include IMP importation and labelling, Patient Information Sheet language requirements, differing treatment practices etc.. Approval of the protocol itself could be separated from approval of subsidiary details, but this would simply move the delay to another point in the process.

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?

All options have merit and do not appear to be mutually exclusive.

Single submission of an assessment dossier (ie, option 3.4.1) appears attractive, particularly if it is coordinated with a centralised dossier submission for NCA authorisation. A single per-country submission (similar to the current UK process) would still be beneficial, but would add far less value.

This development might spotlight the diversity of EC review fees throughout the EU (eg, no fee for review in the UK, fee required in Ireland etc.) and could have wider implications for ECs' organisation and funding.

There would certainly be benefit in strengthening the networks of EC members throughout the EU (ie, option 3.4.2), and facilitating the (non-binding) sharing of best practice. However, this could require significant funding, not least because members take part on a voluntary basis. However, this sharing of operational processes etc. should be entirely independent of the decision-making itself: national ECs could be invited to endorse a common opinion but we would be unhappy to see decreased national scrutiny of clinical trials.

Clarifying the legal scope of assessments (ie, option 3.4.3) can only be helpful and should be taken forward regardless of consideration of the other options. This clarity of scope should also extend to governance/contractual matters.

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

The issues discussed in this section are well recognised.

The over-designation of substantial amendments (4.1.1) is a predictable response to a lack of clarity in what should be considered substantial, as sponsors take a conservative approach in dealing with their uncertainty. A simple list of scenarios could be provided to reduce the size of this "grey area".

The problems arising from the reporting of SUSARs (4.1.2) stem from:

1. Diverging interpretations by NCAs in different Member States of what should be reported, reporting route, timelines etc., leading to
2. A lack of clarity on behalf of sponsors of multinational studies, but also
3. Resourcing issues for NCAs and (particularly) ECs in dealing with the increased volume of SUSAR reports.

The first two of these problems could be improved by more detailed guidance being shared by NCAs on what they consider Serious, leading to greater harmonisation of opinions and greater clarity for sponsors. However, one would expect (and, indeed, hope) that reporting would still be higher than pre-2004 levels. Systems and resources would need to be put in place to alleviate this burden. A lesson could be learned from the ongoing improvements and usage of the EudraVigilance system.

Any clarification of the handling of non-interventional trials (4.1.3) is to be welcomed. However, the intrinsic risk of the trial itself should not be the only consideration when setting the standards of conduct of non-interventional trials and other data-focussed health care research. The ultimate use of the results of the research should also be a factor. This type of research often informs clinical practice and, therefore, robustness of data should not be in doubt.

Other examples include determination of whether a product is or is not a IMP (eg. imaging markers, provocative agents, foodstuffs) and whether a trial is or is not mechanistic etc.

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

Reporting of SUSARs has been beneficial compared with reporting all SAEs; in that sense, the introduction of the SUSAR must have increased participant protection. However, in the non-commercial sector, dissemination of safety information and meaningful signal detection remains particularly difficult. Our contributors have mixed opinions on whether the resultant patient protection is "insufficient" or simply sub-optimal.

We agree that administrative costs have increased significantly as a result, with some contributors suggesting that the increase for non-commercial sponsors is far greater than the 90% quoted.

The high administrative burdens defeat the advantages that reporting SUSARS should bring. Admin costs and time have risen to the extent that they dominate the process. Clinical trials managers do very little science, although they have to be scientists, and spend almost all of their time on administration. These increased administrative costs have been particularly difficult for investigator-led studies and small biotech sponsors.

A link between these issues is that cost modelling plays an increasingly important role in the design and initiation of commercially-sponsored trial protocols, excluding what could have been key participant info and/or dropping key participant populations to reduce administrative costs.

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?

Clarifying the provisions of the Clinical Trials Directive (4.3.1) to reduce scope for interpretation would certainly be expected to improve the situation. Our contributors share the impression is that some Member States interpret the Directive in a more onerous fashion than others, and this is to be discouraged.

At first sight, there is a case for centralising distribution of SUSAR reporting, so that reports are cascaded from the database to relevant ECs. However, this would present further divergence from ICH GCP, under which the investigator is responsible for reporting.

On the basis of reducing scope for divergence and local interpretation, a Regulation (4.3.2) appears to be the preferred option. However, our contributors are concerned that achieving agreement on a final text for such an important document in the form of a Regulation would require protracted negotiation, if it is achievable at all. If it is maintained as a long-term goal, we would still advise proceeding with significant clarifications as an intermediary measure.

It would be hard to demonstrate that the divergent outcomes result entirely from differences in the application of legislation on a case-by-case basis, as there are clear differences in how the Directive is transposed into law in different Member States. A confounding factor is that this transposition did not take place in isolation, but in many Member States was done in the context of existing legislation around the use of medicines etc., minimising or managing

disruption to existing structures and institutions, and alongside other initiatives to improve the competitiveness of individual Member States in attracting global clinical trials.

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

We cannot provide an example of a trial taking place in the EU that HAS applied risk-differentiation, and this is really the issue. The concept of pragmatic application if ICH-GCP is poorly understood. This results in the 'guidelines' rarely being used as such, but applied to the letter, whatever the context of the trial.

Additional examples of insufficient risk-differentiation suggested by our contributors include:

- Use of a licensed product for its licensed indication but, eg, a blood sample is taken to measure a 'marker'. As a result of this, the project is deemed, sometimes inconsistently, a CTIMP with the requirements which this brings.
- Differing expectations of how co-administered therapy should be managed

On a related point, one contributor highlighted that not being able to use a single insurer for all Member States is administratively time-consuming and can be expensive.

10: Do you agree with this description? Can you give other examples?

Our contributors agree with this description, particularly with regard to non-commercially sponsored studies. It is difficult for sponsors, in particular non-commercial sponsors, to take responsibilities for a clinical trial performed in another Member State. Equally, it is difficult for NCAs to enforce the Clinical Trials Directive vis-à-vis sponsors located in another Member State.

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?

We agree that the guidelines should be revised, but suggest that this should not be the only revision.

We suggest that this revision should encompass all types of trial with all types of intervention. They should also help investigators and sponsors in being able to apply a risk-based approach to operations, perhaps by establishing categories or banding to reflect relative risk, based on the nature of the intervention, vulnerability of the participant and the complexity/demands of the trial etc..

One contributor highlights the need to revise guidelines on safety reporting for studies in the non-commercial sector, where often the Sponsor does not own the IMP. This also has an impact on clinical trial authorisation applications, where a non-commercial sponsor would not readily have all the required information on an IMP it did not own.

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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?

We agree that the Directive itself should be reviewed in addition to the various guidelines, but have no further comment on the scale of potential impact.

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

We strongly disagree with the option of excluding academic sponsors from the scope of a revised Directive. Such a regime would be open to abuse. We can't have double standards, but whatever standards we do have must be achievable for all.

The cooperation of academia and industry that is being fostered by national translational initiatives would be hindered rather than helped by a two-tier environment. Data produced under "academic" rules may have lower credibility (presumably this is why results would not be considered in a MAA), which could lead to industry having to repeat trials initially conducted in academic setting, which is undesirable on grounds of both ethics and efficiency of research.

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?

The measures introduced in recent legislation have certainly improved the situation. Nonetheless, we think that paediatric research should be explicitly within the scope of any review, and the transparency and networking initiatives suggested should be explored further.

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

We agree that the issue of emergency research should be explicitly addressed.

Our contributors report that the waiver approach has worked well, although the concept of "legal representative" can cause practical difficulties. Brief, verbal assent has also been used successfully followed by full consent (once the patient is stable) in phase III trials in an emergency setting. This form of post-intervention consent could focus on how data might be used as well as confirming the patient is not averse to being in the trial.

Additionally, emergency studies involving participants from pre-identifiable high-risk group (eg, heart attack victims identified as high-risk following a prior minor attack) could make use of broad canvassing to high-risk groups to raise awareness before an emergency situation arises.

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16: Please comment? Do you have additional information, including quantitative information and data?

We agree on the risks and principles, but note that many sponsors (particularly commercial ones) have rigorous monitoring processes and QC assessments in place to assure all sites in third countries perform to the necessary high standard.

Some third countries are also aware of the risks and are taking action. For example, CA approval for a global study to be conducted in India was given on the condition that no more than 50% of patients would be recruited in India.

In our experience, EU-sponsored trials conducted in third countries are conducted to similar standards as within Europe so some of these concerns are unfounded. However, there is a huge range of practice, much like in academia before the Directive came into force. It is important to keep in mind the range of studies and disease area and the large need for disease management studies in these regions.

It is important to asses how ECs are governed and operate in these countries. Within the EU there are tight regulations on how EC should operate, we should ensure these basic safety rules are also applied in non-EU countries and include evidence of compliance in CSR (clinical study reports) as a minimum.

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

International cooperation and mutual recognition (7.3.3) would be favourable as it would lower confusion over several guidelines and standards. This would be particularly beneficial if such a process could ensure emphasis was placed on pragmatic and appropriate application of guidelines relative to the risk of the protocol

Optional assessment (7.3.4) is already done by the FDA, and has been seen to be successful as long as enough resources and support are provided by the sponsor.

Public registration (7.3.5) could be difficult to enforce and add another level of administration to regions where resources are already limited. There is also the important matter of whether some or all trials would be registered. This could risk two standards of trials, which would be unethical and also cause confusion and risk negative impact on studies being run to answer questions of importance to local public health issues. Any initiatives to improve trial standards should apply to all studies.

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?

There are several other aspects that we would like to see considered.

We are concerned that the current structure discourages creativity in trial design. The majority of a manager's time is spent on regulatory compliance and there is little left for the science. Regulators appear to expect familiar and standardised approaches. In reality, the Directives do not dictate standard approaches, but they have created a culture of standardisation in this sense, while allowing excessive disparity of practice among member states.

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One aspect that causes our contributors problems in academic research is encountered when collaborating with institutions outside the EU. In such circumstances, it is difficult for the EU institution to act as the "Sponsor's Legal Representative" if that renders them legally liable for the other institution's acts and omissions, rather than being a simple "post-box" function.

Another concern is that the requirement for the Chief Investigator/Principal Investigator to be limited to physician, nurse/midwife, dentist or pharmacist causes problems with suitably qualified clinical academics who wish, quite legitimately, to carry out CTIMPs (eg clinical psychologists, non-invasive cardiologists). The list could be broadened with the caveat that a physician should be involved (as for nurses etc.)

We would also like to see a resolution to the question concerning which version of the Declaration of Helsinki should be used.

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The Institute of Clinical Research (ICR) was founded in 1978 as ACRPI (The Association of Clinical Research for the Pharmaceutical Industry). In 2000 it changed its status to become The Institute of Clinical Research and is well established as the largest professional clinical research body in Europe and India. It is a not-for-profit organisation, guided by a Board of Directors who are elected by the membership. Its 5000 members are individuals, working in sponsor organisations, investigational sites and support organisations, engaged in all operational and managerial aspects of clinical research.

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