Comments on the Public Consultation Document
Assessment of the functioning of the 'Clinical Trials Directive' 2001/20/EC

The Clinical Trial Service Unit (CTSU) is part of Oxford University and is an academic unit coordinating a number of large national and international trials including those involving third world countries. Oxford University acts as Sponsor for these studies which are designed and undertaken by CTSU. Funding is obtained from various sources including industry. We welcome the opportunity to comment on this document and broadly agree that there has been a substantial increase in bureaucracy since the introduction of the European Clinical Trials Directive. Problems are caused by both over-interpretation and differing interpretations of the Directive in different Member States as well as the prescriptive guidance in some areas.

Particular points we would like to emphasise in our response:

1. **Risk-based approach to trial regulation:** there should be no differentiation between "academic" and commercial trials, but instead a risk-based approach to the regulation of all trials, as it should make little difference whether the data are to be used for a marketing authorisation or to influence clinical practice. Assessment of the overall "risk" of a trial should relate to the entity being tested, the circumstances in which it is being tested and the size and duration of the study. It would be valuable to have the opportunity for a risk assessment of the trial and planned compliance with the Directive (including the interpretation of potential flexibilities) to be approved by the regulator at the time of starting trial so that sponsors (e.g. University) and funders (e.g. Industry) are fully conversant with the proposed procedures.
2. **Clarification of SUSARs requiring expedited reporting:** there is a need to clarify the definition of a SUSAR in order to avoid over-reporting (which may mask unanticipated adverse effects) and to simplify reporting procedures.
3. **Restriction of substantial amendments requiring approvals:** the definition of substantial amendments to study protocols needs revision to ensure that only those amendments that truly affect patients are included.
4. **Need for appropriate monitoring and audit:** there is a need to ensure that trial monitoring and audit is designed to assess those aspects of trials that really do influence patient safety and data integrity, and not simply largely irrelevant indicators that happen to be easy for a monitor to check.
5. **Need for an option of a 'single dossier' application for multi-centre clinical trial approval** as opposed to assessment of a request for authorisation of a clinical trial being done independently by the NCAs of the various Member States concerned.

Consultation Item 1: Can you give examples for an improved protec tion? Are you aware of studies/data showing the benefits of the Clinical Trial Directive?

One clear benefit of the Clinical Trials Directive in the UK has been the establishment of multicentre Ethics Committees and a single opinion provided for the whole country. By having better trained and supported Committees we believe that this has enhanced patient protection and it has certainly reduced the administrative burden.

Key Issue 1: Multiple and Divergent Assessments of Clinical Trials

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

Yes, as part of a large university which acts as an sponsor for multinational and trials involving third countries we agree that the current system of multiple approvals is time consuming and administratively burdensome.

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

Yes. We agree with all 3 weaknesses described alt hough typically in large trials we work with industry to speed this process.

Options to address the issue as regards assessment by NCAs

Consultation item 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?

We strongly support streamlining the assessment by NCAs to allow them to reach a common agreement in a timely fashion. We would favour 3.3.2.1 option b), a single authorisation for the entire community. The implementation would need to be carefully throughout through and could build on the Voluntary Harmonisation Procedure already in place . If a single authorisation was to be provided within a specified time -frame the planning and management of a trial would be greatly simplified, particularly if Ethics approvals could be sought in parallel.

However, it would not seem appropriate for a single authorisation to be applied to studies which are intended only to take place in a single member state. In such cases the sponsor should be able to choose whether the local NCA or a European wide application is necessary. This should not be related to the type of IMP.

Options to address the issue as regards the assessment by Ethic s Committees

Consultation item 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?

3.4.1 In the UK we have had a succe ssful introduction of a one -stop application process for Ethics and NCA approv al, which has been welcomed by t rialists. However, we do not consider it would be practical or appropriate to have a single opinion for a community wide study givenn local and cultural issues.

3.4.2 More cooperation between national Ethics Committees would be welcomed if it were to lead to:
a) The same dossier of information being provided to a network of committees
a) Streamlining of requirements for the content of Patient In formation Leaflets and the degree to which other patient-related documents (such as patient newsletters) need to reviewed by such committees;
b) Rationalisation of what is deemed a substantial protocol amendment in different countries and which bodies requ ire notification of such amendments.

3.4.3 This would be particularly welcomed as there is substantial overlap at the moment in what is considered by both bodies. We would favour SUSARs only being reported to NCAs and not to ethics committee.

Key Issue 2: Inconsistent Implementation of the Clinical Trials Directive

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

4.1.1. *Substantial Amendments* Yes, this is an accurate description and one of the major issues in the UK where an additional layer of R&D departments require to be informed or even to have to approve each amendment. One particular problem is the requirement for multicentre trials in the UK to submit every new site and change in local investigat or as a substantial amendment , even though such notification is unlikely to affect patient safety . In multi-site trials new sites are commonly accrued throughout the trial well after the initial approval since not all sites agree to collaborate at the same time. In one large multinational trial this has meant that there have been 25 substantial amendments . This has hugely increased the administrative burden even though , as indicated above , the single initial application has been beneficial.

In large complex trials changes to secondary or tertiary assessments and addition or removal of particular blood measurements should not be considered substantial amendments if they do not affect patient safety. A much tighter

definition of 'substantial' would help to ensure that only those amendments that really do affect patient safety are reported in this way.

4.1.2 *Reporting of SUSARs.* Yes, SUSAR reporting is also a problem and is not currently protecting patients as was anticipated. Again careful interpretation of the guidance can minimise the numbers of events that become SUSARs. However, our experience of working with pharmacovigilance staff in pharmaceutical companies is that there is a tendency to use very restrictive definitions of 'expectedness' based on a list of symptoms or conditions without consideration of variations in clinical definitions or presentations. Much more flexibility should be allowed so that different definitions of the same adverse event are treated similarly. There are some trials , such as those involving treatments that have been in use for many years , where it may not even be appropriate to require reporting of SUSARs.
It should also be noted that once an event has been reported as a SUSAR it may be incorporated into the Investigator Brochure/Core Safety Information and thus becomes an 'expected' event. The EU detailed guidance on the collection, verification and presentation of adverse reaction reports (April 2006) states that 'an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important ' should also be reported in an expedited manner. However, in reality this can be difficult to detect due to the absence of good epidemiology for the event concerned, and difficulty in estimating the denominator for the event in the general population.

In the context of large randomised trials an independent Data Monitoring Committee, which is unblinded to treatment allocation, is much better placed to assess whether serious adverse effects are likely to be drug related. The requirement that SUSARs are only reported if the patient was on active medication (in a placebo controlled trial) also leads to large numbers of investigators being unblinded to patient's treatment allocation, which may influence the reliability of reporting of other events.

4.1.3 It does not seem appropriate to include non-interventional studies within the scope of the directive. Given the negative impact of the Directive on intervention trials there is a real danger that these problems will impact on non-interventional studies. Problems with differing interpretations of the guidance in different member states should be dealt with by modification of the guidance rather than by extension of regulation.

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

Weaknesses

SUSAR reporting is particularly relevant to early phase trials of drugs with limited human experience. It is not relevant or likely to be informative for trials of drugs which have been widely used for many years.

The major problem with the current regulations is the uniform reporting requirement for all trials and it is in this area that a risk based approach to safety monitoring would be particularly appropriate and could be carefully specified and agreed upon as part of the initial regulatory approval by NCAs. The obligation to report SUSARs to Ethics Committees should be removed.

The rationale for SUSAR reporting is clearly being misunderstood when cancer (a disease with a known long latency) is reported as a SUSAR in short term studies. Therefore it might be appropriate to redefine which sorts of serious adverse events might be considered drug related and in what context.

Options to address this issue

Consultation item 8: Which option is preferable?

4.3.1 and 4.3.2 We strongly support revision of the guidance documents to allow greater flexibility in the implementation of the Directive. This could be undertaken and lead to improvements rapidly. We do not support the introduction of a regulation which could produce even more rigid application of rules. In the longer term a comprehensive revision of the Directive should be undertaken.

Key issue 3: Regulatory framework is not always adapted to the practical requirements

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

Example: Two trials run by CTSU have been required to have identical safety reporting and drug labelling procedures in order to comply with the Clinical Trials Directive. Both trials have recruited >5000 patients and have unblinded Data Monitoring Committees. One trial involves a new drug combination and the other is assessing extensively studied drugs (aspirin and fish oils). Stringent safety reporting is clearly more important with a new drug. For both drugs the treatments are calendar packed into blister cards and then boxed. It seems extremely inappropriate that the safety reporting requirements are identical for the 2 studies.

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

5.2.2. Sponsor responsibilities in academic led trials are often too varied to be undertaken by a single organisation. This may be particularly true for paediatric

trials or trials of rare diseases. There should be no reason why the responsibilities cannot be delegated to different groups or people as appropriate. At a meeting of the European Forum for Good Clinical Practice on *Innovative Approaches to Clinical Trial Co-Sponsorship in the EU* in 2009, UK researchers present did not consider sponsorship to be a significant issue. [1] However, the implementation of the Directive in the UK essentially allows for co-sponsorship of national trials as opposed to a single sponsor. We would recommend that this procedure/option should be recognised in other Member States throughout the EU.

Consultation item 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?

5.3 and 5.4 Extensive revision of the guidelines could be used to introduce a risk-based approach to drug labelling and safety monitoring including of SUSARs. The revised guidance needs to include flexibility where appropriate and be treated as guidance and not as rules.
Example: One of the most costly requirements in the drug labelling guidance is the instruction that the trial drug must be identifiable to a patient level on the 'immediate packaging'. The effect of this, for calendar packed drugs, is that each calendar pack inside an outer labelled carton (for example) has to be separately numbered usually to match what is on the outer carton. In a large study this may help with drug accountability but it is not clear how this enhances patient safety and is not done in routine clinical practice. The requirement can substantially increase drug packaging costs.

Consultation item 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?

5.4.2 The Directive needs to be reviewed and amended to allow a more risk based approach.

Consultation item 13: Excluding clinical trials of 'academic' sponsors from the scope of the directive.

5.4.3 We strongly disagree with this suggestion. Academic sponsored clinical trials do include those for which the data may subsequently used for a marketing authorisation (for example CTSU's Heart Protection Study), and not allowing academic led trials to be used for a marketing authorisation could be seriously detrimental.

Key Issue 4 Adaptation to peculiarities in trial participants and trial design

[1] http://www.efgcp.be/Downloads/confDocuments/Final%20Programme%20Co-Sponsorship%20Workshop_21%20September%202009.pdf

Consultation item 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.

Trials should be classified according to 'risk'. The first factor in assessing risk should be the relationship between the treatments used in the trial and those that would be used outside the trial. It does not seem sensible to place enormous additional administrative burdens on those entering patients into a trial where the same treatments could legitimately be used for patients not in the trial. This would include, for example, treatments being compared because, although they are regularly used, the frequency of use varies substantially between centres, regions, or countries. It should also include variations in treatment schedules. Other instances might be where a drug had a long history of frequent use but was being tested in a new setting.

Rules on the production and administration of IMPs should not be applied to products already in routine use where the trial treatment question is simply one of scheduling. For example, the non-intensive maintenance treatments in childhood leukaemia are given for 2-3 years, and the children receive the drugs from local hospitals rather than the specialist treatment centres. If we wish to randomise a reduction in treatment (removal of one or two drugs from the schedule) for patients identified as very low risk (by newly available methods) these drugs become IMPs, even though without a trial all patients would receive them and the 'experimental' arm is the one without them.

There is a particular problem with shared care in paediatric trials, which would be alleviated if some arrangement could be made for lesser regulatory requirements in secondary centres that provide the less intensive/experimental parts of the treatments.

'Specials' present a particular problem. Where a trial includes small children special formulations of some drugs have been in use for some time. The use of suspensions, rather than tablets, allows small children to be administered the correct dose more easily. The requirement for these to be handled as other IMPs may lead to centres having to use tablets, and splitting them in order to administer a low enough dose, until either the small companies producing specials attain regulatory approval, or the major companies can be persuaded to produce them.

In some diseases patients are treated at small centres such as district general hospitals which only treat a few patients a year. It is extremely costly to put in place all the regulatory paperwork for a centre which may only enter one patient a year into a particular trial. A system which allowed streamlining /delegation of regulatory requirements for small trial sites would help overcome this.

Consultation item 15: should this issue be addressed? What ways have been found in order to reconcile patient's right and the peculiarities of emergency trials? Which approach is favourable in view of past experience?

It is extremely important that this situation is addressed to allow the continuation of clinical trials in emergency medicine and other situations where fully informed consent is difficult to obtain.

The principle should be that if that patient needs urgent treatment and is not in a fit state to give fully informed consent then treatment needs to be guided by the uncertainty of the managing medical staff. If the medical staff are substantially uncertain about the value of a particular treatment it is entirely ethical for that treatment to be allocated at random (and more ethical than it being given at random). Safeguards can be built into the approval process for such studies to enable the participants to be protected as far as possible.

There are also other situations where there should be flexibility around the way that informed consent is to be sought. For example, some trials are conducted entirely by mail and in future could be conducted via the internet without an interview between investigator and participant. This may be entirely appropriate in some situations and can allow a cost-effective study to be undertaken and should not be rendered impossible by restrictive rules on gaining consent.

Key Issue 5: Ensuring compliance with GCP in clinical trials performed in third countries.

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

We have extensive experience (in particular in China, Thailand, Malaysia and Australia) of running trials in third countries and would consider it the Sponsor's responsibility to ensure that standards of practice are upheld and comparable with elsewhere. Hence we adhere to option 7.3.2. With training and support of staff in third countries we find that compliance with the principles of GCP is very good. There are difficulties when countries, such as Australia, have a slightly different interpretation of GCP and effectively use their own version.

Another consideration is interpretation of GCP in the context of local cultural differences. In some cultures group interaction with professionals is more acceptable than in other cultures producing different norms for obtaining consent and for considerations of confidentiality. GCP is written with the expectation of individuals interacting with professionals but there may be circumstances where group interactions are an acceptable alternative.

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

Options to address concerns about third countries not complying with international standards of safety or ethics :

7.3.1. *Supporting regulatory framework and capacity building* : We support this initiative.
7.3.2 *Self-regulation by EU-based sponsors:* We currently adhere to this principle in running trials in third countries.
7.3.3. *Strengthening international cooperation in GCP inspection and mutual recognition of GCP rules:* Inspections are one of the most burdensome aspects of the current regulations and we would caution about extending inspections to third countries.
7.3.5 *Strengthening a culture of transparency* : Greater transparency and wider registration of clinical trials would clearly be of benefit.
7.3.6 *Strengthening scrutiny of clinical trial results which are submitted to the EU or which are financed in the EU* : It would seem appropriate to know that trials in third countries have been carried out in an ethical and sound manner if the data are being used to support a marketing authorisation in the EU. However, this need not extend to full compliance with GCP but should comply with the principles of GCP.

Consultation item 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?

Other comments:
Inspections One of the features of the Directive has been the introduction of inspections of clinical sites and sponsors by NCAs. The major difficulty with such inspections is the focus on aspects that are easy to inspect at the expense of what might matter more for patient safety. For example, the inspecting against GCP which defines the concept of the trial master file and the requirements for different documents to be present in different places is a particular area of focus. In the current electronic era a single electronic source of documents may be more appropriate, more secure and generally more sensible.
Similarly the GCP requirement of keeping a copy of case report forms at site after the end of the trial is less appropriate in the context of electronic case report forms.