1. **Comments on Rapporteur’s draft report**

Referencing requested areas for comment in email from Hazel Baird 12/02/13

**“Comments regarding the Rapporteur's proposals on achieving transparency of clinical trials results** *(specifically we would like to know whether you consider the proposals go too far, and whether they would, if implemented, create additional work and increased administrative obligations for non-commercial sponsors. We would also like to know if, in practice, you would be able to collate all of the information required for the 'report of clinical trials results' referred to in Amendment 21 on page 18 of the report”.)*

* It is agreed that increased transparency is essential to ensure information of new products is available and to prevent duplication of effort.
* A clinical study report, as defined in ICH E3, is particularly desirable for clinical trials of novel agents where the aim of the trial is to gain a license for the product (i.e. pivotal trials).
* However, a clinical study report is not currently required for all trials falling under the clinical trials directive. To date in the UK a peer reviewed publication and/or summary report has been accepted in lieu of a clinical study report for non-commercial trials

Amendment 51 (page 34) requires a clinical study report (defined in amendment 21 using the ICH E3 definition) at one year after the end of trial date for **all** trials. Registered CTUs have significant concerns with this proposal, which include:

* Production of such reports would be onerous for non-commercial sponsors as they would cause a significant additional demand on resources. One CTU estimates (based on experience of preparing CSRs for pivotal trials) an additional 3 months full-time work would be required. We do not consider that it would be good use of public funds (from NIHR or charities, the usual funders of academic trials) to mandate a full CSR. Financial penalties for non-compliance could also be a concern
* A full report (as defined) would not always be applicable or possible in situations where a trial is abandoned (for example due to poor recruitment)
* In small trials there is also the concern that the data listings required in a CSR might allow deductive disclosure of personal information about participants and thus compromise principles of confidentiality.
* Clinical study reports (as defined) are not always the most useful way for results to be presented and interpreted. We agree that greater transparency is needed but we believe that this can be achieved through trial registration in a publicly accessible database, making clinical trial protocols available, a commitment to always publish the results (with increasing emphasis on open-access publication) and providing a mechanism for other researchers to be able to request (controlled) access to (raw) trial data for legitimate purposes, without imposing the considerable costs of producing a detailed report that would add little value for every trial.
* Phase III academic trials already have robust systems for external scrutiny through the IDMC (independent data monitoring committee) and independent members of the TSC (trial steering committee).  These mechanisms could easily be strengthened and made more transparent through minor modifications to the IDMC and TSC charters, by requiring that both committees sign off the main trial publication (usually an article for publication in a peer reviewed journal) prior to submission.  This would provide assurance that the protocol and statistical analysis plan had been followed and that the paper was a true reflection of what happened in the course of the trial and of the data.

Amendment 53 (page 39) contains an addition that requires all clinical trial information to be stored “in the format of a clinical study report”, however it is not clear how this would be achieved. We suggest a change to: ‘...in a format that will allow data to be easily compiled into a clinical study report’.

Amendment 10 (page 11) – request for clarification: Is the intention that the requirement in recital 20 that “clinical trial data submitted in support of a clinical trial application should be based on clinical trials recorded in a publicly accessible database” would include creation of Reference Safety Information for established multi-drug regimens comprising of marketed products?

“**Views on Amendment 71 re Annex 1 on page 45 of the report** *(we would like to know whether a full statistical analysis plan is already available when the CT dossier is submitted for authorisation, or whether this information only becomes available at a later stage.”)*

A full statistical analysis plan (SAP) would rarely be available at the time of CT dossier submission. The SAP is generally considered to be a separate report which would not be included in the protocol. A SAP is typically amended/developed during the trial and is not usually finalised until prior to the database lock for the main analysis.

It is desirable, as the justification for amendment 71 states, to include information on statistical analyses in the protocol to show how data will be used. Current wording in ICH GCP section 6.9 may be more appropriate than requiring the inclusion of a ‘full statistical analysis plan’. (e.g. *A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).)*

**Other general comments**

Many of the proposed amendments are excellent and we support them. However there are a couple of key areas that we feel greater thought is needed.

The aspiration to have all clinical trials undertaken in the target population (cf trial relevance – page 48) is a good one, but really should only be applied to final stage/phase three studies. It does not reflect the fact that phase 1 studies are undertaken in healthy volunteers or the fact that for example dose escalation studies may need to be undertaken separately for men and women and may only be done a single study at a time. Some of the wording of the proposed amendments in relation to this point also suggest that all sample sizes should be large enough to be able to undertake stratified analysis by age and gender (see below). We feel that is inappropriate to have the directive mandate set subgroup analyses as these should be selected on scientific grounds; this could have a major impact on the size of studies.

The other area that raises issues is the inclusion of the data sets in the clinical trial report. Whilst we are committed to providing open access to our data (and UK-based non-commercial funders such as NIHR, MRC and charities now generally expect a data sharing plan), we would usually do that under a data sharing agreement that ensure that the data was shared for a set purpose, that the purpose is in line with the original consent provided and with an agreement in place not to try and link the data to other datasets which might result in identification of individuals. Therefore we are concerned that putting trial data freely available on the web will meet the aims of improving systematic reviews (including individual patient analyses), but may also result in inappropriate reanalysis, data trawling for sub groups and exploitation by commercial parties for publicity purposes. We need an approach that allows for some access control. Currently the sponsor is the access control – an alternative approach would be to make an application to an independent body, but with justification of use. It is also worth noting that many studies continue tracking patients until death and therefore datasets can be updated for a long time after study closure (and clinical trial report).

It would be good to see encouragement of the protection of vulnerable groups as an area for collaboration. Whilst patients in these groups need protection from exploitation, if the barriers to doing research in them remain high, then they suffer from being research neglected and have an absence of an evidence base for their treatment.

There are a number of places in the report where it is stated that information should be given ideally orally. We think this should be amended to ‘given in the format most accessible to the target population’.

We have some concern about requirements for indefinite archiving. This seems excessive although we do acknowledge that it should be longer than 5 years (many non-commercial sponsors with whom the registered CTUs work have a minimum of 15 years). The lodging of the Trial Master File in the EU portal also raises issues about its public nature (and also requires it to be in an electronic form, which most aren’t currently).

**Any other aspect of the report about which you may have concerns?**

1. **Ethics committees:** justification as to why the Rapporteur has increased references to ethics committees within the report has been provided on page 48 of the document, however whilst we agree that ethical oversight is desirable, it is possible the re-introduction of the references is in places too prescriptive and may conflate the roles of regulatory/competent authorities and of research ethics committees (e.g. proposed amendments 3, 32-34). For example:

* Amendment 2 (page 6) – requires prior ethics approval, in addition to authorisation, even though an ethical review is included as part 2 of the application for authorisation.
* Amendment 7 (page 9) – this is not a problem in the UK but may be in other member states
* Amendment 30 (page 22) – ethics committees would be unlikely to be involved in the part 1 assessment in the UK as the ‘justification’ for this amendment suggests.
* Amendment 33 (page 23) – is the intent here that the REC and CA liaise in coming to their decisions?
* Amendment 34 (page 24) –the issues raised here appear to be the domain/remit of a research ethics committee, rather than a competent authority.

1. **Amendment 4** (page 7) – we do agree that “the rights, safety and well-being of the individual research subjects should” be preserved as far as possible, but the role of the ethics committee is to balance the risk to these individuals against the potential of the research to save lives and improve the health of future generations. There is a significant risk that this change could render it almost impossible to do a phase I or II clinical trial.
2. **Amendment 5: part 1** (page 8) – The stipulation that regarding “ensuring that the group of subjects participating in the trial represents the population to be treated” is a potential issue in all phases of trial. In early phase trials, if the maximum tolerated dose is dependent on sex (e.g. as in the case of quizartinib), then one would want to escalate men and women separately, so the trial may not be equally available. Even late phase trials do not need to be representative; what is important is that they are as generalisable as is reasonably possible, which is a completely different requirement. For example, it might be desirable to include larger numbers of less common types of participant to get more reliable estimates for such subgroups, in which case the trial would be deliberately less representative in order to be more generalisable. Additionally, the cost of including a very broad spectrum of patients (who may eventually receive the treatment) may delay introduction of a beneficial treatment in the vast majority of patients Furthermore, it is not possible to legislate that the consent rate is equal across different groups; the trial can be made equally available to relevant people (however you describe that) but if fewer women consent, is this a problem – it seems to be according to a literal reading of this. This amendment could also be interpreted to mean that one can’t open trials in larger centres only, as they do not necessarily represent the people treated in district general hospitals. Furthermore what does this clause mean for trials in healthy volunteers? Might there may be circumstances in which the target group are not be able to consent, but the question could be answered with a non-target group who could consent?
3. **Amendment 5:part 2** (page 8) – as not all sponsors are the manufacturer of a product, and as a systematic review may already have been undertaken by others, we suggest the text added is amended as shown below:

*In order to ensure that the clinical trial is relevant, the sponsor should, where possible, provide* ***or refer to*** *a systematic review of the existing data on the investigational medicinal products.*

It was further suggested that, since a ‘systematic review’ is a very specific research tool that may not be appropriate or feasible for all IMPs, that the phrase ‘systematic review of the existing data’ be replaced by ‘comprehensive review of the published literature’ or ‘comprehensive review of the existing evidence’.

1. **Amendment 11** (page 12) – as per comments on the previous page, there is a risk that unrestricted access to raw trial data may result in a correctly done study being subsequently incorrectly analysed for promotional purposes. Such an analysis may then be billed as an analysis of the original trial, despite it never being originally intended and it may have no scientific validity. Such access can also create a whole industry of data dredgers.
2. **Amendment 12** (pages 12-13) – it was felt that the phrase ‘additional protection measures’ was unclear, and needed to be defined here or elsewhere.
3. **Amendment 13** (page 13) and **Amendment 45** (page 29) – we feel that the emphasis on oral presentation is misplaced. Whilst we agree that discussion of the trial is desirable, depending on the nature of the trial and the study population, pictorial/diagrammatic or other formats may be required or more appropriate than simply an oral presentation. We recommend that the focus should be on the provision of information in the best format to optimise understanding of that particular trial and in that target population. We also have concerns that the requirement in all circumstances for individual consent to the intervention (as opposed to being included in the trial and providing data) may be a barrier to the conduct of cluster randomised trials (including stepped wedge designs) in which the unit of allocation and intervention delivery is a group of individuals (e.g. a hospital ward or geographic community). This type of design may be the most appropriate for some vaccine or chemopreventive efficacy trials (examples of both cluster randomised and stepped wedge CTIMPs can be provided).
4. **Amendment 14** (page 14) – we recommend that there be a requirement to update the start and finish dates in the trial register as needed, since these (particularly the end date) may change from what was originally planned.
5. **Amendment 16** (page 15) – clarity needed on whether “their use does not fall within normal clinical practice” refers to normal clinical practice only within the Member State in question (we assume this is the case), or in any Member State.
6. **Amendment 17** (page 16) – Two points to be made here: (a) we feel that ‘low intervention’ trials would perhaps be better named as ‘low risk trials’ with the definition extended to trials testing established treatments with good safety profiles for novel uses that are not standard practice (e.g. aspirin for cancer prevention); (b) greater clarity is needed about what is meant by ‘sufficient published evidence’, especially in the absence of an explicit treatment guideline.
7. **Amendment 21** (page 18) – it was queried whether there should be provision to modify the requirements (particularly in respect of safety data) in the case of low intervention trials, in line with the regulation’s aim of proportionate regulation.
8. **Amendments 23** (page 19), **26** (page 20) and **42** (page 28) – it may be advisable to provide an operational definition for ‘quality of life’ since this term is used variably; does it imply that a validated measure of quality of life should be used?
9. **Amendment 25** (page 20) – the suggested additional text (“allowing for a stratified analysis by age and gender”) could be interpreted to mean that all trials should be powered for a pre-specified sub-group analysis by gender and age(group). This could have significant implications for overall sample size and therefore the cost of the trial. Is this the intent of the suggested modification?
10. **Amendment 27** (page 21) – the proposal for informed consent requirements to be assessed in part 1, as well as in part 2, would seem to be an unnecessary duplication.
11. **Amendment 34** (page 23) – we feel that there would be value in seeking the views of the relevant patient groups (or their advocates/representatives) as well as those of professionals. We query whether ‘… or after taking advice…’ should read ‘… and after taking advice…’.
12. **Amendment 38** (page 25) – needs to be clearer about what is meant by ‘conducted prior to the date of this regulation’; does this mean started before this date, or started and finished before this date.
13. **Amendment 39** (page 26) – the removal of ‘principles equivalent to those of’ should be reinstated. Clinical trials run in third countries cannot be required to have complied with ‘this Regulation’.
14. **Amendment 45** (page 30) – is ‘otherwise that information may be given in writing’ needed in the sentence?
15. **Amendment 48** (page 32) – we suggest that (as the justification states) the ‘outcome’ of the trial should be made available to the subjects, rather than subjects being provided with the ‘results’. We also note that many of our lay representatives suggest this should be a choice not a mandate – i.e. that subjects should be given the choice of receiving the results or not as they prefer. The information also needs to be in an accessible format (i.e. not a scientific paper). We query whether there needs to be a timeframe for the provision of this information.
16. **Amendment 52** (page 35) – suggest that ‘shall’ be modified to ‘may’, which appears to be more in line with the justification that the Member States ‘should be entitled’ to enforce a penalty.
17. **Amendment 53** (page 34-35) – the implication of this proposed amendment appears to be that a trial that is temporarily halted for 12 months will not start again; is this the intent? We advise that IMP supply issues can drag on for over 12 months. In these circumstances, a report on the database could break the blind. This actually has the potential to be a breach of equipoise. If it is fair to assume that the trial will start again after 12+ months, interim results should not be out into the public domain, as this would create problems with later approval as it would represent a breach of the statistical analysis plan. We therefore query whether it is in fact the data or a clinical trial report that should be submitted? It is our view that it should be a report, specifying the reasons for stopping and undertaking any analysis that could be planned (but only if the trial is not to be resumed).
18. **Amendment 56** (page 37) – this could be interpreted to mean that the sponsor doesn’t have sufficient resources to run a trial (in which case they should not be doing so!). Perhaps a better wording would be ‘in some circumstances it may be sufficient to inform the Agency instead of the marketing authorisation holder’? We also felt that the justification should focus on suspected unanticipated serious adverse reactions (SUSARs) rather than all suspected serious adverse reactions, regardless of expectedness.
19. **Amendment 57** (page 38) – we suggest replacing ‘becoming aware of that breach’ with ‘a transgression has been positively identified as a (serious) breach’.
20. **Amendment 60** (page 39) – the proposed requirement for ‘indefinite’ storage for all trial master files (TMFs) would seem excessive and presupposes that the Sponsor continues to exist in perpetuity. It would significantly increase the resources needed. While we agree that storage for longer than the current 5 years is desirable, some limit (e.g. 15 years) seems a reasonable compromise. This amendment also suggests that master files can be archived in the EU database. The majority of TMFs are still paper based and as regulatory requirements for wholly electronic storage are onerous and not widely applied, we query whether this is practical?
21. **Amendment 61** (page 40) – if each area of responsibility can be split between multiple sponsors, the specific remit of each of those sponsors will need to be explicitly and unambiguously documented, to avoid duplication or (worse) some activities not being covered by any sponsor.
22. **Amendment 68** (pages 43-44) – we recommend inserting ‘relevant’ between ‘all’ and ‘existing evidence’ to avoid the risk of all applications being tracts based on out of date/low relevance evidence.
23. **Amendment 69** (page 44) – we suggest adding ‘or their representatives’ after ‘patients’, since in some circumstances (e.g. paediatric trials or those in individuals lacking capacity) the involvement of patients themselves may be neither possible nor appropriate.
24. **Amendment 72** (page 45) – greater clarity on whose conflicts of interests (the sponsoring organisation? all individuals named in the protocol? all investigators?) and what comprises a relevant CoI is desirable.
25. **Amendment 73** (pages 45-46) – we note a frequent tension between the requirement for information provided to be ‘consistent with statutory information’ and the needs and preferences of patients and their representatives; patients and their advocates are often dismayed and confused by long participant information sheets, which follow REC guidance on content but are overly burdensome to read and process.
26. **Amendment 74** ‘(page 46) – as with amendment 69, we recommend adding ‘or their representatives’. Need to ensure that those giving consent for others (e.g. parents, legal representatives) are included too.

**General comments (on rapporteur’s report)**:

* 1. the change from ‘incapacitated persons’ to ‘incapacitated subjects’ in amendment 12 also applies in other areas, e.g. recital 22
  2. Addition of ‘or the legal representative’ after ‘subject’ is not always consistent, e.g. recital 24, needs ‘subject or their legal representative’

**Comment on NHS European Office report**

* **Amendment 2** – is this intent here that clinical studies include studies/trials of non-drug interventions (e.g. surgical
* **Amendment 11 –** Further update is needed to article 39 paragraph 2 to clarify end of annual reporting obligations when the situation in the second paragraph of the two paragraphs proposed in amendment 10 apply (i.e. one report allowed per clinical trial, rather than per IMP).

**Additional comments on text of the EC proposal regulation**:

* Suggest clarification as to whether references to timelines as ‘days’ refer to ‘calendar days’ or ‘business/working’ days.
* Recital 36 – suggest ‘**where applicable**’ is added at the end of the recital. Justification: Investigator Brochures are not required for all investigational medicinal products.
* Article 2 – paragraph 2, point 18 – suggest clarification that this refers to ‘legal representative **of the subject’** to differentiate from other uses of ‘legal representative’
* Article 35 – request for clarification, should the final sentence state: “...shall **each** be considered as a substantial amendment”?

1Contributing CTUs: CR UK and UCL Cancer Trials Centre; MRC CTU (London); Newcastle CTU; Cardiff CTUs (HCTU Cardiff, SEWTU, Wales Cancer CTU), CRCTU Birmingham, CTSU Oxford, Barts CTU, NWORTH (Bangor).