PERSONAL RESPONSE TO

ASSESSMENT OF THE FUNCTIONINING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC PUBLIC CONSULTATION PAPER.

Consultation Item no 1.

I am not aware of any examples.

Consultation Item no 2.

In addition to the increased cost and difficulty, trials have been severely delayed by the directive and this delay is unethical, delaying results of trials for parents, patients and children.

Adapting a protocol as suggested is necessary (and is necessary to obtain permission from a CA) is exactly what having one sponsor was supposed to prevent. Having more than one protocol means more than one trial within the trial: this is very dangerous since such divergence will not be picked up by anyone – even at the publication stage if only one protocol is submitted for review then the existence of other protocols will not be visible. And which is the "master" protocol?

Consultation Item no 3

An additional impact is the effect on trials of rare conditions. Rare conditions still account for highly significant morbidity and mortality. Yet multiple sites in several countries are required to recruit sufficient numbers of patients. This means that the cost of bureaucracy and administration is much, much higher per patient than for common conditions – yet it is easier to obtain funding for common conditions for obvious reasons. Yet some rare conditions account for very high economic cost per patient and therefore significant economic cost to the EU that might be prevented by clinical trials.

Consultation Item no 4

Please remember that a Marketing Authorisation may not cover all participants or all indications and currently may vary from Member state to Member state.

Consultation Item no 5

It is not improving the ethics of trials to have multiple assessments. My current trial had a patient information sheet of 11 pages required in the UK. This was felt by our parent representatives to be so long as to be unethical but we were unable to challenge it. In Australia, we were required to shorten it to 5 pages to obtain approval. This illustrates the need for harmonisation that should lead to a one stop shop for ethics approval being possible – and much preferable. This is a major issue causing increased cost, delay and leading to different patient information sheets in different Member States – hardly reasonable for the participant.

Consultation Item no 6

In the UK, it is considered a substantial amendment if you add a site. In trials with many sites, it is not possible to delay a start until all sites are ready. In addition since on average 7% of PIs will change each year, and each is considered a substantial amendment many amendments result. None of these improves patient safety. As long as the sites are known (and PIs known and approved locally) why does the CA need to know? The information can be given by the sponsor very quickly in the unlikely event

that it is known (or the sponsor can be required to notify but not as a substantial amendment).

Not only are multiple SUSAR reports happening, but it is difficult to believe that they result in a proper assessment of trial safety by an independent body. Certainly the ethics committees do not have the expertise to assess this yet they have to be told. Why?

Another example of confusion is with the use of Phases for describing trials. The clarity of the definition begins to fall apart when you consider if a treatment is being used "off label". A medicine may be licensed for a condition but not for combined use with another licensed medicine. Is this off label? Do you start again at Phase 1 since first use in man of the combined treatment may be happening? In our trial some medicines are licensed in some EU countries for the condition being studied but not in others so the CA makes a different decision about the Phase of the trial. This does not make sense and the use of Phase should be dropped in favour of a risk assessment.

Consultation Item no 7

The consequence of the Directive is that my two trials of a rare epilepsy, one conducted prior to the Directive and one subsequent to it, show an increase of nearly 3 times in Staff employed, a huge increase in time to get sites able to recruit (more than double) that is in part due to the directive. This increases bureaucracy of the assessment and running of the trial at each site. There is much duplication of effort with each site undertaking their own assessment of whether the trial meets Directive criteria.

Consultation Item no 8

A regulation would be by far the best result since a Chief Investigator and the Sponsor would know what was expected throughout the EU. And without translation I presume.

Consultation Item no 9

I would comment that some trials use medicines from the normal supply route since for a variety of reasons, the medicine is not given blind (ie masked as to treatment allocated). In this case, medicines already approved with a marketing license are available with normal labelling. Thus the huge additional cost of labelling and tracking is not necessary yet some bodies interpret the Directive as requiring this. While in the UK, the use of special modalities allows the MHRA to give exemption from labelling this is only where "they are used on patients with the same characteristics as those covered by the authorised indications". The interpretation of "same characteristics" and "authorised indications" leaves too much room for disagreement. I would suggest instead, " where the risk assessment based on the characteristics of the participants and of the usual treatment for these participants suggests that specific trial labelling is not required".

Consultation Item no 10

I would add that with trials with sites outside the EU, other sponsors will have to be part of the trial since they will usually be required in those other countries. If that is acceptable, why are we required to have one sponsor within the EU when that makes life very difficult indeed for academic non commercial sponsors?

Consultation Item no 11

I am not aware of EudraLex Volume 10 and can not comment.

Consultation Item no 12

I would recommend a Regulation not a change to the Directive

Consultation Item no 13

The disadvantage of excluding academic sponsors (while otherwise attractive) would mean that national rules would apply. This would maintain the bureaucracy of such trials in many member states and this consultation should result in significantly reduced bureaucracy. A method of providing for a one stop review of such academic or non commercial trials, if excluded, is strongly advised.

Consultation Item no 14

I would add an additional problem caused by the fact that many trials in very young infants require follow up to determine developmental outcome. The treatment phase of the trial would have long ceased, yet because the patients are followed up this period is considered part of the trial. The problem is put into stark relief if you consider the situation where an earlier developmental follow up has shown such results that further follow up at a greater age is now required but was not originally part of the trial. Such a plan would not require a new clinical trial approval but the initial follow up would have been considered part of the trial.
I would recommend a clear statement that the follow up period after treatment with trial medicines is NOT part of the trial and does not need to be treated as such.

Consultation Item no 15

Since this is an ethical issue, the Directive should not have interfered and made it difficult to do emergency trials. It should be adjusted to remove this problem.

Consultation Item no 16

Please remember that third countries may not be developing ones and may have very good control of trials – such as Australia. And that central monitoring is a proven way of detecting fraud and is much cheaper (and therefore best for academic or non commercial trials). A response proportionate to the risk is advised.

Consultation Item no 17

Reduced requirements for academic or non commercial trials. Automatic approval for countries demonstrating similar standards to the EU – for example Australia.

Consultation Item no 18

- Uniform nomenclature is required. For example, in some countries, principal investigator is the term for the senior investigator for the trial while this usually refers to the senior investigator at one site with Chief Investigator being the senior investigator for the trial.
- Why are some member countries requiring investigators to repeat GCP every 2 years? What is the proof this is necessary? Can this be in the Directive or Regulation at a lower frequency – perhaps 5 years. There is no proof of the value of current training anyway, and this

requirement does make life difficult for PIs in rare conditions where good support from the trial centre is more appropriate.

- Please can the EU commission require official translations into all member state languages – at present unofficial translations cost each trial huge sums and delays and may not be accurate.
- A major problem is the requirement to provide medicines free to the trial participant. This may make sense when the participant is not unwell, does not need treatment and where they would be at a disadvantage if the treatment had to be paid for. However, for a condition that must be treated anyway in a Member State where the participant would otherwise have to pay for the treatment, providing treatment free is an inducement to take part and therefore unethical. This needs urgent attention.

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