

Response to the European Commission consultation to assess the functioning of the Clinical Trials Directive 2001/20/EC

The National Health Service (NHS) is one of the largest publicly funded healthcare systems in the world providing the majority of healthcare in England. The NHS is committed to the principle of universal access to healthcare which is free at the point of use. Every 36 hours the NHS sees over one million patients who make use of a wide range of health services ranging from primary care, in-patient care, long-term healthcare, ophthalmology and dentistry. The NHS is a major employer in Europe with more than 1.3 million people on its payroll.

The NHS has a strong history in clinical trials and, through its structure and access to patient databases can play a vital role in the uptake of innovative new medicines and technologies. Furthermore clinical trials in the UK have made a large contribution to improved healthcare delivery around the globe and there continues to be enormous research potential in the NHS with academic and commercial partners.

In recent years however, the UK has lost ground internationally as a leading clinical trials environment. A 2009 UK government report¹ showed that the UK's involvement in global clinical trials dropped dramatically from 6% in 2002 to 2% in 2006, while the percentage of EU products in clinical trial development in the UK fell from 46% in 2002, to 24% in 2007. In addition end of year figures for 2009 from the UK Department of Health indicate that the number of mid-stage, late-stage and post-approval clinical trials fell from 728 in 2008 to 470 in 2009, its lowest level in the past decade. Early stage trials fell to 210, the lowest in five years. There is an urgent need to improve the climate for clinical trials in the UK. It is our view that a review of the existing EU Clinical Trials Directive can help us to achieve this.

This response has been coordinated by the NHS European Office² in consultation with NHS organisations.

Consultation response

Key Issue 1: Multiple and divergent assessments of clinical trials

NHS organisations felt that the Consultation paper presented an accurate description of the current situation with regards multiple and divergent assessments of clinical trials.

Streamlined procedures

While there was some divergence of views as to whether a voluntary harmonised procedure for clinical trials or full harmonisation across Member States would be more effective, NHS respondents agreed on the need to establish an EU-wide streamlined approach to clinical trials. In addition, any mechanism to improve clinical trials processes should enable faster approval of

¹ Review and refresh of bioscience 2015, published January 2009. <http://www.berr.gov.uk/files/file49805.pdf>

² The NHS European Office was launched in September 2007. It represents the English National Health Service. Its role is to inform the NHS of EU issues and to ensure that the NHS contribute positively to EU developments.

clinical trials and avoid being open to different interpretation by the national competent authorities in different member states.

With regards a mutual recognition procedure it was proposed that the clinical trial authorisation (CTA) process in each participating country should be evaluated in order to ensure that minimum standards for CTA apply within that country.

With regards a fully harmonised system, there was support for procedures being applied in a limited way, applying only to multinational trials or to certain categories of trials.

Ethics Committees

NHS organisations would support greater cooperation between ethics committees in Member States and further legal clarity of the respective scope of assessment by NCAs and Ethics Committees. There is clear support for a one-stop-shop approach as regards the submission of the request for authorisation of a clinical trial to the NCA and Ethics Committee. Respondents agreed that this would reduce the administrative burden of multiple submission of information to separate actors, and would speed up the approval process.

Respondents also emphasised the need to maintain national independent ethical reviews and local practices with regards information provided to patients / potential subjects of clinical trials.

Key Issue 2: Inconsistent implementation of the Clinical Trials Directive

NHS organisations felt that the Consultation paper presented an accurate description of the current situation with regards inconsistent implementation of the Clinical Trials Directive.

Substantial amendments

Respondents supported the need for clarification around the definition and management of substantial amendments. This would provide consistency across countries and should reduce the burden of reporting, given that some sponsors are over-classifying amendments as substantial.

Adverse incident reporting

NHS organisations agreed that reporting of serious adverse reactions (SUSARs) has increased since the implementation of the current Clinical Trials Directive, and that this is a disincentive to engage in clinical trials. Clarifying the procedures and modalities of reporting SUSARs to the Community database would restrict the scope for variations in interpretation of the law and would improve the current situation.

Concerns were raised about the identification of SUSARs and the definition of what adverse events may be expected during a given trial. Many investigators do not realise the importance of such information in ensuring that SUSARs are truly unexpected events rather than those which may reasonably occur, especially in trials where individuals are not in good health when enrolled. This is a point of education at national and regional level. Inappropriate reporting of SUSARs may be avoided where appropriate information has been provided prior to the trial taking place.

In addition it is suggested that the end of trial notification report requirement be adapted to reflect the outcome data of the main trial endpoints when these are available. At present a 'final

report' is required one year after a clinical trial has ended, however in some cases results of clinical trials may take several years to emerge, for example in studies relating to chemotherapy for early breast cancer.

Interventional and non-interventional trials

NHS Respondents agreed there is a need to find a common interpretation between EU countries in defining the boundary between interventional trials and non-interventional trials. The inclusion of non-interventional trials within the scope of the Directive was not supported by NHS organisations as this approach would result in more and unnecessary bureaucracy.

Options to address these issues

NHS organisations support clarification of the Directive to reduce ambiguity and to make it time and cost effective for bodies engaged in clinical trials. While a Community Regulation may reduce the scope for differences in interpretation and implementation across the Member States NHS organisations largely supported proposals to revise the existing Directive. However any related costs and additional bureaucracy must be kept to a minimum and patient safety must be at the core of any review.

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

The problems identified in the consultation paper are accurately described.

Risk-based approach

Under the current functioning of The Clinical Trials Directive broadly the same requirements apply to all trials, for example, with regards to safety reporting and insurance requirements, with little or no flexibility for variation depending on the level of risk involved. Applying the same approach to trials with varying risk levels is a barrier to research and a disincentive to engage in clinical trials. NHS organisations would support a revision of the existing implementation guidelines. This would allow the Directive to take a more flexible approach which considers the risk of the trial to the patient, information already known about the trial treatment, and the research questions being addressed. In this way the application of the Directive can vary according to the level of risk assessed within the trial.

Requirement for a single sponsor

The existing Directive is based on the principle that there should be a single sponsor per clinical trial. This creates problems in practice for multinational trials, as it is difficult for a sponsor, particularly those from non-commercial and academic sectors, to take responsibility for trials in other countries. The increased amount of work and costs associated with doing this acts as a powerful disincentive to academic and non-commercial led trials, and limits their ability to participate. As a result some studies are simply not carried out. The requirement for a single sponsor can also be difficult for a national competent authority where they may be required to take action against a sponsor based in another country. Changing the requirements with regards a single sponsor to allow a sponsor for each country for multinational trials and reviewing insurance requirements in line with risk should be a priority when reviewing the Directive. The view was put forward by some respondents that clinical trials should allow for co-sponsorship, with an table of agreed responsibilities for each country.

IMP labelling

One NHS organisation with specific expertise in the field of cancer treatment pointed out that a significant proportion of the clinical trials they carry out test IMPs used within their marketing authorisation against IMPs that are licensed but being used in a different indication. The drugs concerned are available routinely from hospital supplies, do not require special manufacture and packaging and are often dispensed in the same way as for standard clinical practice. However, despite this, Annex 13 labelling is required. If the drug is dispensed from a community pharmacy, Annex 13 labelling is waived. This places an unnecessary burden on hospital pharmacy departments.

We therefore recommend that Annex 13 labelling is not required for drugs that are routinely used in standard practice, regularly dispensed from hospital or community pharmacy stock and that are administered by the healthcare practitioner (rather than by the patient themselves).

Excluding academia

NHS organisations would not support the exclusion of clinical trials carried out by academic sponsors from the scope of the Clinical Trials Directive. An exclusion would lead to each country setting its own rules for clinical trials carried out by academic sponsors. This would cause confusion, and make multinational academic-sponsored trials more difficult to carry out, with classification difficult for some studies, for example commercially-funded studies managed as academic trials. In addition an exclusion of academia from the scope of the Directive would prevent the results of academic-sponsored trials from being used to support a marketing authorisation application. The methodology and risk-assessment behind a research proposal should determine which guidelines a clinical trial should adhere to, rather than the type of sponsor.

Options to address these issues

The NHS supports a review of the Clinical Trials Directive, particularly with regards safety reporting, reviewing insurance in line with risk and the requirement for a single sponsor.

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

The NHS would support proposals to adapt the Clinical Trials Directive to facilitate and promote special types of clinical trials. NHS organisations agree that it is appropriate to establish requirements to ensure the interests of special patient groups, such as children and patients in emergency care, are taken into consideration in the design and conduct of trials. There may be value in a common EU system to clarify how specific categories of trials should be carried out. Any future mechanisms should not however, create further approvals and documentation, and a proportionate approach to risk and ethical soundness must be central to the process.

Key Issue 5: Ensuring compliance with good clinical practices in clinical trials performed in third countries

NHS organisations share the concern that clinical trials carried out in third countries may not always meet with good clinical practice standards, for example with regards participant safety issues and data quality.

There is support for an EMEA mandate to ensure that good clinical practices are enforced in third country trials, and for greater scrutiny by European regulators of clinical trial results submitted to them, for example as part of a CTA or marketing authorisation application. Some NHS organisations expressed the view that any country wishing to participate in a multinational clinical trial must have incorporated the EU Directive or equivalent standards into their own national law.

Alternatively third countries could have the option of becoming part of a good clinical practice approved group following an EMEA inspection. A similar practice already exists in the UK, under the mandate of the UK's national competent authority, the MHRA. Finally it was noted that the European Commission should have a responsibility to investigate the practices of clinical trials receiving financial support from EU funding programmes.

Attempts to raise the standards of clinical trials in third countries should consider specific challenges individual countries may be facing. Reasons may include lack of interest, lack of time, lack of resource, lack of understanding, all of which would require different solutions. Ultimately there should be support for assistance to third countries where the regulation of clinical trials is currently weak. This would lead to strengthened international cooperation in good clinical practice inspection activities and mutual recognition of GCP rules.