motor neurone disease association

RESPONSE TO CONSULTATION: ASSESSMENT OF THE FUNCTIONING OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC

INTRODUCTION

Few conditions are as devastating as Motor Neurone Disease (MND). It is rapidly progressive in the majority of cases, it is always fatal and it kills five people every day in the UK. It can leave people locked into a failing body, unable to move, speak or eat normally. The intellect and senses usually remain unaffected. There are around 5,000 people living with MND in the UK. Half of people with the disease die within 14 months of diagnosis. There is no effective curative treatment.

The MND Association is the only national organisation supporting people affected by MND in England, Wales and Northern Ireland, with approximately 90 volunteer-led branches and 3,000 volunteers. The MND Association's vision is of a World Free of MND. Until that time we will do everything we can to enable everyone with MND to receive the best care, achieve the highest quality of life possible and to die with dignity.

The MND Association funds biomedical and healthcare research, including clinical trials, and actively works with partner organisations across the EU and beyond to strive for our goal of a World Free of MND. In addition to this role, we act as a source of information for people with MND on existing and upcoming industry-sponsored trials. It is therefore of great importance to us that the regulatory framework for clinical trials should be based on reasonable principles and as simple as possible to navigate. We welcome the opportunity to respond to this consultation, and hope that it will lead to an enhancement of the position of clinical trials in the EU.

Where we do not respond to a specific consultation item, we have no comment to offer on that issue.

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

We are not aware of any data or studies showing either improved protection or other benefits of the Directive.

Consultation item n°2: Is this an accurate description of the situation? What is your appraisal of the situation? [Multiple and divergent assessments of clinical trials]

Our experience suggests that there has not been a decrease in clinical studies, but that there has been a decrease in clinical drug trials.

A series of articles in *The Financial Times* newspaper on December 30 and 31 2009 reported a decline in the number of clinical drug trials conducted in Britain, making use of official Department of Health figures. Early-stage trials fell to just 210 - the lowest figure in five years - and the number of mid-stage, late-stage and post-approval clinical trials fell from 728 in 2008 to 470 in 2009 - the lowest level in the past decade. Increased costs and bureaucracy are a significant factor in this reduction.

Consultation item n°3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences? [NCAs, first patient in, delays]

Increased costs and other difficulties associated with inconsistent interpretations of the Directive by different member states have a disproportionate impact on research into rarer conditions, in two respects. Most MND-related trials are multi-centre, and indeed multi-state, because of the relatively low prevalence of the condition. Obstacles that arise from different interpretations and understandings of the requirements of the Directive occur not only in different member states, but also in microcosm between different centres within the same member state. These difficulties therefore disproportionately obstruct research into rarer conditions.

Increased costs tend to affect smaller pharmaceutical and biotech companies the most, which in turn affects research into rarer conditions most heavily. Smaller companies find it harder to raise the additional investment required during the many years it takes to get a product to market – if indeed it gets that far. As smaller firms are more likely to make products for smaller and more niche conditions, the increased costs for clinical trials disproportionately affect research into rarer conditions such as motor neurone disease.

A related point applies to large pharmaceutical companies: although they can generally afford to bear extra costs, this redoubles their focus on developing products that will ultimately yield very high amounts of income. This means that they tend to take the strategic decision not to make significant investment in developing drugs for rarer conditions.

Consultation item n°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? [Options to address the issue as regards NCAs]

Assessment by a single body at Community level would, on balance, be preferable. Selecting a single member state and then applying their assessment to all others could become needlessly political, and also risks merely delaying the point at which different interpretations of the Directive become a problem. A single, central interpretation and authorisation would remove these difficulties. It could also have the advantage of engendering greater consistency between different centres – whether in one member state or many – in the conduct of clinical trials: at present

the variables between different patient groups in different trial centres, such as different standards of care, can introduce 'noise' into the results of a trial. A single authorising body may assist in providing a greater element of consistency in this respect. Such a body would also certainly make it easier to amend and develop processes around the conduct of trials in light of experience.

Any such authorisation body must, however, be well-resourced and transparently run, to avoid becoming a bottleneck for clinical trials.

We would support the option of this process being used only for multi-state trials. It would be preferable for single-state trials to continue to be authorised at member state level, as these systems are now in place and increasingly well-understood.

Consultation item n°5: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need ton be considered in further detail? [Options to address the issue as regards Ethics Committees]

A one-stop-shop for submitting authorisation requests to all the necessary Ethics Committees could well be helpful from a purely procedural perspective.

We are sceptical, however, about the prospect of success for closer collaboration between Ethics Committees. The range of differing cultural sensibilities within the EU has the potential to make any such exercise extremely difficult. Two examples of ethical issues not directly related to clinical trials will illustrate this.

We are aware that in some EU member states, medical treatment focuses on extending life irrespective of quality of life; in cases of MND, this can involve invasive ventilation to keep a patient alive for a long time, even after they have reached a state of total paralysis such that they are unable to interact or communicate with anyone or anything. In the UK, treatment more often seeks to maximise quality of life, and this sort of invasive ventilation is unusual, and viewed by many people with MND, carers and care professionals as deeply undesirable.

Similarly there are large variations in animal testing restrictions among EU member states, with the UK having arguably of the toughest regime of all. While these examples are not directly pertinent to clinical trials, they illustrate the difficulties that could arise from trying to achieve consensus on ethical issues.

Consultation item n°6: Is this an accurate description of the situation? Can you give other examples? [Inconsistent implementation as regards substantial amendments, SUSARs, and scope]

We have certainly had experience of difficulties associated with amendments to trials. The MND Association is currently funding a clinical trial to investigate the effects of lithium carbonate in treating the progression of MND. A second trial of lithium carbonate was commenced in the USA at the same time, but was subsequently aborted for reasons unconnected to the UK trial.

As news of the American development spread among people with MND in the UK and elsewhere, the trial investigators would have preferred to have contacted all participants in the UK to offer them reassurance that it did not affect their involvement. This would, however, have counted as a substantial amendment to the trial and required ethical approval accordingly: even though the news of the American trial spread across the world within a matter of hours via the internet, it would have taken two weeks before the necessary amendment could even be considered, in order to issue an official communication.

At a time when information can be disseminated so quickly and so easily, a restriction that prevents official communications in relation to clinical trials being made in a similarly short timeframe cannot possibly represent a sensible or reasonable imposition. We urge that changes be made to remove such hindrances.

Consultation item n°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?

On balance, we feel that the option of re-casting the Directive as a regulation, with sensible amendments, would be preferable. This option would reduce the difficulties that arise from inconsistent interpretation and transposition across member states, and also mitigate against possible gold-plating in the event of the Directive simply being revised.

A suitably revised Directive would still be acceptable, however, and preferable to no change at all.

Consultation item n°13: Would you agree to this option and if so what would be the impact? [academic sponsor exemption]

Such an exemption could make academic involvement in multi-state projects more difficult, as the regulatory frameworks governing them in different member states would diverge further. It may be beneficial for single-state trials, however.

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