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

THE RESPONSE FROM UNIVERSITY COLLEGE LONDON

UCL as Trial Sponsor

University College London is at the centre of one the largest partnerships of academic medicine and care provision in Europe. To support the activities of this partnership, the College sponsors of some 91 academic clinical trials.

The UCL portfolio consists of trials in four main categories

- Phase one, proof of concept studies of new drug entities, in particular new biologicals (12% of the portfolio).
- Trials of combinations of licensed drugs mainly in cancer (43%)
- Trials of licensed drugs for new indications (28%)
- Trials of drugs within licensed indications (11%)

Unlike many UK sponsors, UCL still sponsors international trials. Nine UCL sponsored trials are international in that they have sites in Europe and a further five are being conducted with collaborators in US. Only a small part of trial activity (12%) involves new drug entities developed by UCL. This is only part of the portfolio where there is any potential for direct economic gain for the University. The majority of UCL portfolio consists of trials, undertaken by UCL clinicians, to provide innovative improvements to treatment for their patients. Such trials are either publicly funded or funded by charities such as CR-UK.

With such a large, complex and international portfolio, UCL is probably one of the largest and most influential academic sponsors in the UK, if not Europe.

Items 1 -

UCL is not aware of any studies or data which show the benefits of the Directive.

Items 2, 3, 4 and 5.

The consultation document refers to the need to improve the harmonisation of approval processes. UCL supports any arrangements which would reduce the differing national requirements for trial approval.

The consultation also asks for quantification of impact of different aspects of the Directive. It is disapppointing that so little centrally collected data which monitors the impact of the appears to be available. For example, more use could be made of administrative dataset collected in CTA applications. Could this dataset be made publicly available ?

Obtaining data to assess the impact of the Directive on the academic sector is not straightforward. Prior to the UK regulations coming into force, UCL did not centrally collect any information on trial activity. As this is likely to be the case for many academic institutions, comparison of trial activity before and after the Directive needs to be treated with caution.

Item 6 and 7

UCL agrees that the difficulties detailed in the document are an accurate reflection of the inconsistencies in implementation of the directive.

As regards requirements for pharmocovigilance, it is disappointing to find that the data is of such little value, particularly as reporting is such a time consuming activity for our sector. In addition, the reporting framework appears to have little conceptual coherence in trials which use drugs with well know safety profiles or use combinations of IMPs. The lack of coherent rationale for the required safety reporting devalues the activity.

Item 8

UCL believes that any options to address weaknesses in the Directive need to take into account the different characteristics of the commercial and academic sector. Trial activity in the academic sector is either publicly funded or funded by charitable donations. In addition, there is little potential for economic gain for most trial activity in the sector. Instead most trials are undertaken by clinicians to advance treatment options for their own patients and not for the purpose of obtaining a Marketting Authorisation. Thus the types of trial conducted and economics of the sectors are fundamentally different.

The primary driver for the Directive 2001/20/EC is considered to be the technical harmonisation or standardisation of trial conduct, with improving the safety for trial participants as a secondary concern[12]. The purpose of introducing such standardisation was primarily economic - to avoid the

[1] Feick J (2005) *Learning and interest accommodation in policy and institutional change: EC risk regulation in the pharmaceutical sector* ESRC Centre for the Analysis of Risk and Regulation LSE Discussion paper 25

[2] Vogel D (1998) The Globalisation of Pharmaceutical Regulation Governance: *An International Journal of Policy and Administration* vol 11 pp1-22.

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inefficiences which arise when the commercial sector was required to undertake trials to slightly different national standards to obtain a Marketting Authorisations in different EU countries. The standards adopted in the Directive appeared to be based on the presumption that a trial will use single IMP and that there would be little data about the efficacy or safety of that IMP. But the consultation paper suggests that between 20 and 40% of trials take place outside the framework of such an authorisation. Similarly, only around 10% of our portfolio fits the purposes for which the Directive was framed. For the majority of trials sponsored by UCL, compliance with such standards, framed for a different purpose, is only inefficient and expensive.

The lack of flexibility in the standards also adds layers of additional complexity to the conduct of trials with international collaborators, particularly those outside Europe. For example, UCL has collaborations in the US to explore the use of existing licensed drugs in the treatment of rare neurological conditions such as Non-Dystrophic Myotonia. The aim of this trial is develop innovatory treatment for this rare conditions, secure in the knowledge that the benefits of the drug outweigh the side effects. Yet, such trials are extremely complex and costly to set up as they require reconciliation of both EU and US regulations and standards with detailed legal and contractual arrangements.

Item 9 Insufficient risk differentiation

Common standards are not conducive to tailoring the trial management according risks inherent in the IMP or the participant group. The following two cases provide examples of where there have been considerable escalation of costs for trials which are low risk to participants. Both studies were funded by small charities whose objectives are to improve treatments for patients with specific conditions, in the one case leukemia, and in the other, Inflammatory Bowel Disease. The negative impact of the Directive on the capacity of such charities to fund trials is considerable.

> Case 1: G-CSF is a naturally occurring hormone used in pharmacological doses to boost the production of haemopoietic stem cells of donor origin for bone marrow transplantation. From 2004 onwards there have been a few publications reporting that the administation of G-CSF to normal donors resulted in unwanted chromosomal changes. The Anthony Nolan Trust is a medical charity that recruits volunteer donors to provide stem cells for bone marrow transplantation to patients with leukaemia or other haematological disorders. The ANT staff wished to study whether the adminstration of G-CSF according to their usual protocol did in fact result in chromosomal changes. The study involved simply taking an extra aliquot of blood for analysis. There were no other changes to usual harvesting regimen. However, the study was classed by MHRA as a trial requiring a Clinical Trials Authorisation and therefore the costs to the charity of conducting the trial doubled.
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> Case 2. Aloe Vera is plant extract which is sold in "over the counter" in UK pharmacies for a variety of purposes including use as a food supplement. A clinician at UCL proposed to study the use of Aloe Vera as a suppository in inflammatory bowel disease. The US manufacturers of Aloe Vera agreed to donate the product for the Trial but as Aloe Vera was to be used as an IMP there was a requirement to comply with EU regulations on importation of IMPs. UCL found a QP who was willing to release the product. But the manufacturer refused to co operate as they could not understand the need for the further requirements as exactly the same product formulation was imported and sold as a food supplement in UK. Had the manufacturer agreed, the

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costs of QP release would have been considerable. More importantly, patients and other can continue to ingest Aloe Vera, yet the regulatory requirements and their economic effects preclude clinicians from systematically evaluating its effects.

In general, the costs for trials which are unlikely to have economic gain for the University have escalated. In 2003 UCL employed two staff working on trials other than in cancer and in 2010 this had increased to 10 including specialists posts in pharmacy, contracting, pharmacovigilance, monitoring and regulatory affairs. UCL has found it difficult to recoup these costs from charities and other public funders and trial activities have had be supported by the Universities' central funds.

Item 10

UCL does not accept that multi sponsorship is less problematic than single sponsorship. UCL has had some experience of multi sponsorship in trials in collaboration with US and where there are no sites in EU. Our experience leads us to conclude that multi sponsorship is problematic. The difficulties lie in the apportioning legal liabilities between institutions and, following from that, the insurance arrangements. Much time and effort can be wasted negotiating liabilities between sponsors. Moreover, UCL has been advised by specialist insurance lawyers that the contracts need carefully drafting with the full involvement of all the sponsors' different insurance companies. Otherwise, sponsors risk the insurer refusing any claim because overlapping cover.

Item 11,12,13,14,15

The consultation document asks for comments on revision of various guidelines. However, for the academic sector, the problems are rather more fundamental. The Directive has been primarily designed to address the problem of harmonisation of trial conduct in context of a Marketting Authorisation. The rules and standards have therefore been framed for a particular of type of trial - that is a trial designed for purpose of obtaining a MA. The majority of trials sponsored by UCL are not for this purpose and the requirement to comply with rules designed for other purposes is inappropriate and inefficient.

Clinical trials are the means of legitimating two types of innovations in medicine. Innovations which have purely social benefits and those which may have economic utility. Drug development takes place through a synergistic relationship between pharma and clinical medicine. Clinical academics often take the products from drug companies and further refine them to the economic benefit of the industry. This may occurr without much initial interest or support from pharmaceutical sector. The development of the first chemotherapeutic agents occurred in this way[3]. The costs now involved in sponsoring such unsupported activities risks disrupting this relationship, thwarting innovation within medicine and drug development in general. This may have consequences for the economic competiveness of the commercial sector.

If there are concerns about the safety of academic trials then a move away from command and control regulation to other regulatory designs would be of benefit to the academic sector. Reframing the regulatory problem for the sector in terms of controlling innovation rather than

[3] Flowers CR and Melmon KL (1999) Clinical Champions as Critical Determinants of Drug Development in Landau R, Achilladelis B and Scriabine A (eds) *Pharmaceutical Innovation Revolutionizing Human Health* Philadelphia Chemical Heritage Press

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standardization might lead to a different set of arrangements where greater attention was paid to mechanisms which as well as fostering participants safety, fostered conditions necessary for learning, knowledge transfer and entrepreneurialism For example, a form of "enhanced self regulation" would promote the self management capacities of professions or academic institutions. Instead of requiring compliance with prescriptive standards, this form of regulation would ensure that institutions have robust systems in place for participant safety. This would force institutions to innovative to control their own risks.

To ensure that any regulatory changes do not have counterproductive effects on both the development of these social benefits and the long term future of innovation within the pharmaceutical industry, the Commission should engage with the sector in the design any change. Moreover a detailed on going assessment of the effects of such changes needs to undertaken.

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