ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

18 August 2016

Science and Technology Committee
House of Commons
London
SW1A 0AA

RE: Written Comment Submitted by the Association of Clinical Research Organizations (ACRO): ***Inquiry on Leaving the EU: implications and opportunities for science and research***

Dear Committee members:

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through pivotal studies assessing the safety and effectiveness of new products – as well as post-approval and pharmacovigilance research. With 9,000 employees engaged in research activities in the UK, over 33,000 in Europe, and more than 120,000 worldwide, ACRO member companies advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 pharmaceutical, biotech, and medical device sponsors of clinical trials each year.

Clinical research today is a global and pan-European enterprise. As with academic research, clinical drug development research knows no borders. Pharmaceutical companies and CROs have a growing number of geographical options for the placement of clinical studies and seek out receptive business environments characterized by regulatory certainty, harmonization, consistency, and predictability.

Measured by both CRO employment and clinical study placement statistics, the UK plays a vital role in clinical research compared to other European countries. The results of ACRO's 2013 biennial survey of its members showed that, at that time, ACRO member companies employed 9,418 staff in the United Kingdom, compared to 5,337 in Germany, 2,483 in France, 1,967 in Spain, and 1,584 in Italy. In 2013, ACRO member companies placed more clinical trials in the UK and Germany (1,320 and 1,321 respectively) than in France (1,086), Spain (1,046), or Italy (926).

As the Committee navigates this period of transition, ACRO believes the following measures will help ensure this continued vitality of the UK life sciences industry:

1. Continued implementation of the EU Clinical Trial Regulation 536/2014
2. Continued implementation of the General Data Protection Regulation
3. Maintaining a close working relationship between the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA)
4. Maintaining the free movement of clinical research professionals and clinical trial specimens and samples

I. Continuing implementation of the EU Clinical Trial Regulation 536/2014 in the UK is vital for business and for the UK economy

The regulation of clinical trials in the EU is soon set to change considerably with the full implementation of the EU Clinical Trial Regulation 536/2014[1] and the harmonization of the regulatory authority clinical trial approval process. In order to continue to be an attractive venue for clinical trials, ACRO believes the UK should maintain on ongoing relationship with the EU that allows the implementation of the EU Clinical Trial Regulation 536/2014 to continue in the UK in a timely fashion. At the very least, ACRO recommends establishing an effective process in the UK for the mutual recognition of clinical trial approvals granted by EU member states, together with collaboration with EU member states on post-approval surveillance and pharmacovigilance of clinical trials. The alternative – i.e., a country-specific clinical trial approval and surveillance system – would simply add cost and delay, and reduce the regulatory attractiveness of the UK for clinical research.

The European Medicines Agency (EMA) web site characterizes the key benefits of the new Regulation[2]:

- *Harmonised electronic submission and assessment process for clinical trials conducted in multiple Member States*
- *Improved collaboration, information-sharing and decision-making between and within Member States*
- *Increased transparency of information on clinical trials*
- *Highest standards of safety for all participants in EU clinical trials*

ACRO believes that the UK should strive to ensure that these benefits are maintained in the UK in order to continue to present an attractive environment for clinical research that supports the principles of harmonization, consistency, and predictability.

The goal of the EU Clinical Trial Regulation 536/2014 is to harmonize the clinical trial application and assessment process across Europe. However, there are two sections within the Regulation that are so broad and vague that they could be interpreted and implemented in dramatically different ways across the member states – *thereby thwarting the Regulation's goal of European harmonization and, thereby, the consistency and predictability that business relies on*. Since the adoption of the Regulation in 2014, ACRO has advocated to both the European Commission and across the Member State national competent authorities for specific, clarifying interpretations of these two key sections of the Regulation: Article 74 and Annex 1. The currently vague language in these sections can be easily clarified to create predictability and consistency for industry. As detailed in the Appendix to this letter, ACRO encourages the UK to interpret these two sections in order to create an environment that fosters clinical research.

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[1] Regulation (EU) No 536/2014 (Official Journal of the European Union, 27.5.2014)
http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

[2] European Medicines Agency web site
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp&mid=WC0b01ac05808768df

Article 74 of the Regulation states that biopharmaceutical companies ("sponsors") that are located outside the EU must establish a "Legal Representative" in the EU and that this Legal Representative *"shall be responsible for ensuring compliance with the sponsor's obligations pursuant to this Regulation."* This requirement is so unclear and impractically broad that it could be interpreted and implemented in wildly divergent ways across the member states – creating disharmony, inconsistency, and unpredictability. ACRO has been advocating for an interpretation of Article 74 that would maintain the harmonizing intent of the Regulation. ACRO's argument to the European Commission, individual member states, and now the UK on the interpretation of Article 74 are detailed in the Appendix to this letter.

Annex I of the EU Clinical Trial Regulation 536/2014 introduces brand new requirements for clinical trial protocols. The protocol must now contain a description of the "arrangements" or "measures" to protect personal data. However – as with the requirements of the "Legal Representative" in Article 74 – what would qualify as an adequate arrangement or measure is so unclear that it could potentially create disharmony, inconsistency, and unpredictability in its interpretation across the member states. *As the UK implements these requirements, ACRO recommends an interpretation of Annex I that explicitly recognizes "key-coding" (or "pseudonymization") as an adequate and appropriate arrangement for the protection of personal data.* ACRO's argument to the European Commission, individual member states, and now the UK on the interpretation of Annex I are detailed in the Appendix to this letter.

II. Continuing implementation of the General Data Protection Regulation in the UK is vital for business and for the UK economy

The regulation of data protection is also undergoing significant harmonization in the EU at this time with the introduction of the General Data Protection Regulation[3] as well as the recent publication of the EU-US Privacy Shield to facilitate movement of personal data between the EU and the US. Maintenance of a regulatory system of data protection that is harmonized between the UK and EU is critical to ongoing clinical research if the UK is not to lose ground in this field after leaving the EU.

In our opinion, the UK should also continue to implement the General Data Protection Regulation. A country-specific data-protection regime could reduce the regulatory attractiveness of the UK for clinical research. A country-specific regime would also prove more difficult for the UK government in terms of demonstrating adequacy with EU requirements and could potentially prove disruptive to the transfer of clinical research data between the UK and EU member states. This again could reduce the competitiveness and attractiveness of the UK for clinical research. Additionally, a country-specific regime would potentially increase the likelihood of future regulatory drift from EU requirements, again leading to issues of adequacy assessment.

While ACRO believes that it is vital for the UK to continue to implement the EU regulatory regimes for clinical trials and data protection, we recognize distinctive national tax policy is an appropriate competitive tool. ACRO commends the UK for tax policies that promote innovation. In particular, the structure of the Research & Development tax credit encourages the employment of well-paying clinical research positions and places the UK at a competitive advantage to most other European countries as well as the United States. We strongly urge the UK to maintain these policies, or strengthen them, to maintain its competitive position after leaving the EU.

[3] Regulation (EU) 2016/679 (Official Journal of the European Union, 4.5.2016) http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=en

III. Future relationship between the MHRA and the EMA

The Medicines and Healthcare Products Regulatory Agency (MHRA), the national regulatory authority for medicinal products and medical devices in the UK, has had a significant position in the London-based European Medicines Agency (EMA). Inspections, product assessments & scientific advice by the MHRA on behalf of or in conjunction with the EMA have contributed significantly to drug development and clinical research in the EU. Separation of the UK from EU institutions seems most likely to also entail the loss by MHRA of membership of EMA. There is a risk of consequent divergence of regulatory approaches and procedures in key areas of drug and medical device research development. Any such changes are likely to have a detrimental effect on clinical trials and clinical research in the UK.

ACRO suggests that the MHRA seek to maintain a close working relationship with the Good Clinical Practice Inspectors Working Group (GCP IWG) of the EMA, and continue the current practice of conducting clinical trial site inspections together with regulators from other EU member states, while at the same time developing relations and agreements with key regulatory bodies outside the EU (e.g., the US Food and Drug Administration) to facilitate the mutual recognition of clinical trial inspections.

The MHRA benefits from its relationship with the EMA. The MHRA receives income from the EMA for medicines assessment, scientific advice, and inspections undertaken on behalf of the EMA. In 2014-15, this amount was 10.5 million pounds, and in 2013-14, the amount was 9.3 million pounds.[4] ACRO encourages the Committee to consider funding to make up for this loss to ensure that MHRA is fully funded and staffed in order to fulfil its important duties.

Similarly, the EMA benefits from its relationship with the MHRA. As noted in a study from the European Federation of Pharmaceutical Industries and Associations (EFPIA) entitled "Assessing the impact on the life sciences industry of a change in the UK relationship with the EU," the MHRA is one of the most active and vital contributing national competent authorities to the EMA because it is the *top* rapporteur for EMA assessment according the EMA's 2014 annual report. [5]

IV. Concerns regarding the movement of staff, IMP, samples, and specimens

In this era of the global clinical trial, consistency of standards, approach and requirements greatly facilitates clinical research and permits the conduct of multi-centre, multi-national clinical trials. At present, the EU facilitates the free movement of people, goods and services involved in clinical trials (e.g. clinical trial professionals, clinical trial investigational medicinal product (IMP) and clinical trial specimens and samples). To maintain the attractiveness of the UK as a location for clinical research, strenuous efforts should be made to preserve the unhindered movement of clinical research professionals and products. The UK should seek to minimize cross-border administrative paperwork which could impose costs and delays.

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[4] MHRA Annual Report, 2014-15
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/448091/Annual-Report-2014-15.pdf

[5] "Assessing the impact on the life sciences industry of a change in the UK relationship with the EU"
http://www.efpia.eu/documents/216/61/Assessing-the-impact-on-the-life-sciences-industry-of-a-change-in-the-UK-relationship-with-the-EU

If cross-border movement of clinical research professionals becomes more difficult and time-consuming – whether it is the movement of EU citizens into the UK or the movement of British nationals into the EU – then, the placement of multi-national clinical trials at UK research sites may well diminish.

To summarize, ACRO recommends that:

- *The UK continue implementation of the EU Clinical Trial Regulation 536/2014*
  Continuing implementation of the EU Clinical Trial Regulation 536/2014 would provide the regulatory certainty, harmonization, and predictability that is vital for business and for the UK economy
- *The UK continue implementation of the General Data Protection Regulation*
  Continuing implementation of the General Data Protection Regulation would provide the regulatory certainty, harmonization, and predictability that is vital for business and for the UK economy
- *The UK enable the strong relationship between the MHRA and the EMA to continue*
  The MHRA and EMA enjoy a mutually beneficial relationship that needs to be preserved
- *The UK safeguard the free movement of people and products that business requires*
  The free movement of professional staff, IMPS, samples, and specimens provides the certainty and predictability that is vital for business and needs to be safeguarded

These issues are just some of many components of much wider discussions for the UK and the EU in relation to a) co-ordination of European and UK legislation, b) mutual recognition of systems, process and institutions between the UK and the EU, c) movement of people, goods and services between the UK and the EU.

In conclusion

The decision to leave the EU could have unintended negative consequences on clinical research in the UK if not carefully managed. We hope that during the negotiation process the Committee will have the opportunity to vigorously represent the case for clinical research.

As a major stakeholder, ACRO asks to be consulted early and represented in any and all discussions that could impact the future conduct of clinical research in the UK and the EU.

Please contact ACRO (knoonan@acrohealth.org) if we can support the Committee in any way – including providing additional information or expert testimony.

Respectfully submitted,

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Vice President, Global Regulatory Policy

Attachment: Please see Appendix on next page

Appendix

I. ACRO advocacy to the European Commission, the individual member states, and the UK on Article 74 of the EU Clinical Trial Regulation 536/2014:

Article 74 ("Legal representative of the sponsor in the union") states:

> *Where the sponsor of a clinical trial is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative. Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to this Regulation . . .*

ACRO believes that the responsibility for a sponsor's compliance with the Regulation does not shift from a non-EU sponsor to a legal representative under Article 74(1). It would be sufficient for a legal representative to oblige the non-EU sponsor to comply with the Regulation in the contract between the legal representative and the sponsor. Whilst the legal representative is not expected proactively to monitor the sponsor's compliance with its obligations under the Regulation, if the legal representative becomes aware of a situation involving the sponsor's non-compliance, the legal representative should immediately raise this with the sponsor for the sponsor to remedy promptly. A legal representative cannot be held responsible for actions of a sponsor over which it has no control, unless national legislation specifies otherwise.

II. ACRO advocacy to the European Commission, the individual member states, and the UK on Annex I of the EU Clinical Trial Regulation 536/2014:

Annex I ("Application Dossier for the Initial Application") of the Regulation introduces brand new requirements for clinical trial protocols. The protocol must now contain a description of the "arrangements" or "measures" to protect personal data. However, what would count as an adequate arrangement or measure is entirely unclear. As the UK implements these requirements, ACRO recommends an interpretation of this text that explicitly recognizes key-coding as an adequate and appropriate arrangement or measure that would provide the regulatory certainty industry seeks. Below is the original text, with ACRO's recommended interpretation added in and highlighted.

> (ak) a description of the arrangements to comply with the applicable rules on the protection of personal data of subjects; in particular organizational and technical arrangements such as key-coding that will be implemented to avoid unauthorized access, disclosure, dissemination, alteration or loss of ~~information and~~ directly identifiable special categories of personal data of subjects processed;
>
> (al) a description of measures such as key-coding that will be implemented to ensure confidentiality of ~~records and personal data~~ identity of subjects
>
> (am) a description of measures that will be implemented in case of data security breach affecting directly identifiable special categories of personal data of subjects in order to mitigate the possible adverse effects to subjects