

10 October 2018

## **ACRO Response to**

### ***House of Commons Health and Social Care Committee Inquiry: Impact of a No Deal Brexit on Health and Social Care***

#### **Introduction**

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 specialised services across the entire spectrum of development for new drugs, biologics and medical devices from discovery, pre-clinical, proof of concept and first-in-human studies through post-approval and pharmacovigilance research. With more than 13,000 employees engaged in research activities in the United Kingdom (and 57,000 in Europe and 130,000 around the world), ACRO members advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries, including over 1,300 clinical trials conducted in the UK. On average, each of our member companies works with more than 700 research sponsors annually.

Since the result of the UK referendum on leaving the EU was announced, ACRO has worked closely with ABPI, BIA and other industry associations in developing the UK-EU life sciences transition programme. ACRO supports the joint ABPI/BIA submission to the Committee's inquiry on behalf of the life sciences industry. Consequently, ACRO's response to the inquiry focuses on the likely impact of a no deal Brexit on the core biomedical research services that ACRO member companies provide.

#### **Likely impact of a no deal Brexit on biomedical research, including risks to patients and to the health and social care system**

In the event of a no deal Brexit, the UK will be a 'third country' outside the EU. EU legislation will no longer apply in the UK and the UK will not be eligible for participation in EU organisations. The UK will have to address this situation by adapting or creating its own domestic systems. Currently, as a result of EU membership, the UK is integrated in the EU regulatory networks for medicines and medical devices, including the European Medicines Agency (EMA). In the event of a no deal Brexit, the UK's participation in the European regulatory networks will end and the Medicines and Healthcare products Regulatory Agency (MHRA) will take on functions currently undertaken by the EMA.

Clinical trials are regulated nationally and UK clinical trial applications involving medicines and medical devices will continue to be authorised by the MHRA and UK ethics committees post-Brexit. However, new electronic systems for the submission of a single clinical trial application dossier to all EU member states that will be included in the trial, followed by a single coordinated review of the application, are being developed by the EMA (for trials of medicines) and the European Commission (for trials of medical devices and *in vitro* diagnostic devices). Current plans indicate that these systems will go live shortly after the UK's exit from the EU. As a 'third country', the UK will be unable to participate in these new processes and is likely to become a less appealing location for clinical trials in Europe (access via a single application and review to the required patient population in a total population of 466 million people in the 27 EU countries is likely to be favoured over access to a UK total population of 66.5 million). In a worst case scenario, the UK would no longer be selected by clinical trial sponsors for participation in multinational clinical trials in Europe, impacting the UK innovation base, the opportunities for UK researchers to conduct trials in the UK and for patients to participate in them. At the least, sponsors may give a lower priority to applications for clinical trials in the UK compared with the EU27, resulting in delayed access to participation by UK researchers and patients in innovative research.

Recently, the UK government has issued several technical documents that set out the arrangements that will be applied to the regulation of medicines, medical devices and clinical trials in the UK in the event of a no deal Brexit. ACRO welcomes these arrangements, which we believe represent a helpful and pragmatic approach to maintaining capacity and standards for biomedical research in the UK. The UK government, however, will have no control over arrangements that are put in place by the EU in a no deal scenario and ACRO has a number of concerns in this regard, which can be summarised as follows:

#### *Product supply*

Approximately 40% of investigational medicinal products (IMPs) used in clinical trials in the EU are manufactured in the UK (information from ABPI). In a no deal scenario, any additional requirements, costs and/or customs delays to export IMPs to the EU27 would likely result in transfer of manufacturing capacity from the UK to the EU27. Similarly, increased requirements, costs and/or delays in receiving supplies into the UK from EU/EEA manufacturers would have a significant impact on all parties (researchers, patients, clinical trial sponsors and CROs) involved in biomedical research in the UK. The UK government has written to pharmaceutical companies in the UK to urge stockpiling of medicines in preparation for a no deal Brexit. This is much less easily done in the case of IMPs used in clinical trials, as batch sizes are typically much smaller than for marketed medicines, batches are produced less frequently, product labelling is specific to the individual trial, and randomisation of trial treatments (i.e., random allocation of participating trial subjects to either the test medicine or a comparator product) means that treatment packs are specific to individual subjects. Additionally, IMPs comprising radiopharmaceuticals or which are based on gene or cell therapy may have very short shelf lives. Any interruption in the supply of IMPs to UK patients would have a significant impact on the treatment of those patients and the integrity of the research, and in extreme cases could lead to suspension of treatment and of the trial.

### *Batch testing and release of IMPs*

Under EU law, manufacturers can test medicines (finished products) for batch release purposes anywhere in the EU, EEA or other third countries with whom the EU has a mutual recognition agreement. Batch release testing is also an important step in the quality control process for commercial and IMP supplies and sponsors sometimes outsource this capability to ACRO members. The UK government has stated that, in the event of a no deal Brexit, the UK will continue to accept batch release testing of IMPs that is performed in the EU and EEA states, and third countries with whom the EU has a mutual recognition agreement. In the absence of any formal Brexit agreement, however, it is likely that the EU would not accept batch testing performed in the UK. This would result in the transfer of analytical tests, skills and job positions from the UK to laboratories in the EU/EEA. As around 70% of IMPs used in clinical trials in the EU are currently batch-released in the UK (information from ABPI), these losses could be significant.

### *Relocation of expert roles and responsibilities to the EU27*

EU law requires that the following expert roles are located in the EU: a Qualified Person responsible for the batch release of medicinal products (including IMPs used in clinical trials), a Qualified Person to confirm (by signing a GMP declaration) equivalence to EU GMP standards for IMPs manufactured in third countries, a Qualified Person/Responsible Person for pharmacovigilance (for IMPs and marketed medicinal products), a legal representative of a non-EU sponsor (for medicine, medical device and *in vitro* diagnostic device clinical trials), and a representative of a non-EU data controller or processor. Many of these roles and positions are currently located in the UK and, under a no deal Brexit, would need to be transferred to the EU27, leading to a loss of expertise and potential career advancement pathways from the UK.

### *Testing of clinical trial samples*

Thousands of human tissue and body fluid samples for clinical trials and test articles (active substance and/or product) are transferred between the UK and the EU each year for further processing, analysis or archiving. Many of these shipments are time-sensitive, due to sponsor or regulatory timelines or the inherent instability of the samples. In a no deal scenario, any additional requirements, costs and/or customs delays to export samples to or import from the EU27 would reduce the attractiveness of the UK for clinical research, and result in the transfer of analytical tests, skills and job positions from the UK to laboratories in the EU/EEA.

### *Transfer and analysis of clinical trial data*

Just as for clinical trial samples, pseudonymized patient data generated in clinical research are routinely transferred between the UK and EU and other countries for analysis, reporting and archiving. In its recent technical document on data flows in a no deal Brexit, the UK government notes that current practice, which sees personal data flow freely from the UK to the EU, would continue because the UK Data Protection Act 2018 and European Union Withdrawal Act 2018 incorporate the EU General Data Protection Regulation into UK law. However, changes would occur where personal data are transferred from organisations in the EU to the UK. In the absence of formal EU recognition that UK law is adequate to ensure the same level of personal

data protection as required by EU law, the technical document identifies the use of standard contractual clauses as the most relevant alternative legal basis for transferring personal data from the EU to UK (these are a series of model data protection clauses, approved by the European Commission, that enable the free flow of personal data when embedded in a contract between the parties concerned). However, the validity of standard contractual clauses is currently under consideration by the Court of Justice of the European Union and may not necessarily be relied upon as a useful means of securing data transfer in the future. EU law provides several mechanisms that would allow for the transfer of data from the EU to the UK; currently, these include standard contractual clauses, binding corporate rules, certification, codes of conduct and approved *ad hoc* contractual terms. However, a recently published study by the European Parliament's Policy Department for Citizen's Rights (*The future EU-UK relationship: options in the field of the protection of personal data for general processing activities and for processing for law enforcement purposes, 24 August 2018*) concluded that these mechanisms are "generally resource intensive and unsuitable to set up a broad framework for data exchanges that can be used to organise compliance transfers of personal data on a large scale, including particularly regarding SMEs". A considerable administrative and bureaucratic burden would be placed on any organisation (both public and private) adopting any of these measures. However, without doing so, organisations would be unable to transfer clinical trial data from the EU to the UK. Currently, a significant amount of data analysis and reporting for pan-EU clinical research takes place in the UK. A no deal Brexit would likely result in the transfer of this activity from the UK to the EU27, with consequent loss of business, skills and jobs in the UK.

#### *Loss of collaboration with the EU regulatory networks*

EU law requires that adverse reactions to medicinal products are reported to a central EU pharmacovigilance database that covers both marketed products and IMPs in clinical trials. A similar EU database is to be developed for medical devices. However, in a no deal scenario, the loss of UK involvement in these databases and integrated EU vigilance processes would impact the quality and coverage of the systems used to detect side effects and manage safety issues in the UK, and may compromise the safety of UK patients. Additionally, any limitation in MHRA resource capacity could result in potential delay in responding to pharmacovigilance issues, with serious implications for the safety of UK patients and competitiveness of UK clinical research. EU law also requires that, during the assessment of a marketing authorisation application for a medicinal product, it is verified that clinical trials supporting the application (whether conducted in the EU/EEA or in third countries) have been conducted in accordance with required ethical and Good Clinical Practice standards. This requirement, which is continued in UK law through the European Union Withdrawal Act 2018, is met by means of inspecting the conduct of clinical trials for compliance with Good Clinical Practice and ethical standards, and inspecting the manufacture and control of IMPs for compliance with Good Manufacturing Practice standards.

Current UK participation in EU inspection programmes will end in the event of a no deal Brexit and the MHRA would be required to verify compliance of clinical trials submitted to support marketing applications in the UK, without having access to inspection results conducted by other member state regulatory agencies on behalf of the EU. Again, any limitation in MHRA resource capacity to take up this additional workload may impact the quality of regulatory decision-making in the UK, with consequent implications for patient safety and the reputation of the UK. Further, any delay in UK regulatory approvals for new medicines as a result of MHRA inspection delays would reduce the attractiveness of the UK market for novel and innovative pharmaceuticals.

### **How effectively are stakeholders planning for a no deal Brexit?**

Since the result of the UK referendum on leaving the EU was announced, ACRO has been working closely with ABPI, BIA and other industry associations in developing the UK-EU life sciences transition programme and has been active in presenting the ACRO position to UK government. ACRO has consistently advised its member companies to make all necessary preparations for all possible outcomes from the Article 50 negotiations, including the UK leaving the EU without a deal from 29 March 2019. Each individual ACRO member company is preparing in the best way possible that reflects their individual circumstances and the services that the company provides to sponsors in the biopharmaceutical industry. All member companies have undertaken business continuity planning for a range of scenarios, including a no deal Brexit. Examples of the activities that companies have planned for in the event of no deal include detailed assessments of IMP supply to ensure, as far as possible, maintenance of supply to patients, clinical trial approval amendments, legal representative / responsible person planning and transfer, transfer of product testing and release, transfer of the Qualified/Responsible Person roles for batch release and pharmacovigilance, and preparations for increased data processing and reporting in the EU27. In some cases, the successful transfer of analytical methods to another laboratory can take several months to ensure consistency of results and, in such cases, technology/testing transfer is already underway to ensure continuity in the event of a no deal Brexit from 29 March 2019.

ACRO member companies and the sponsors they work for continue to focus on doing everything they can so that clinical research can continue without disruption to patients or researchers after 29 March 2019. However, there are a range of factors outside of our control, including potential delays at border crossings between the UK and EU, and the actions and behaviours of other actors in the clinical research process and associated supply chains. ACRO continues to recommend to both the UK government and the European Commission that the best way of ensuring that there is no disruption is for the UK and EU to agree the terms of the Withdrawal Agreement to allow the implementation period to come into effect, alongside a future relationship that includes cooperation on the various regulations impacting clinical research.

**How effectively does ACRO consider the government is planning for a no deal Brexit?**

ACRO welcomes the recent technical documents published by the UK government, setting out the arrangements to be applied to the regulation of medicines, medical devices and clinical trials in the UK in the event of a no deal Brexit. We consider the arrangements described in these documents represent a helpful and pragmatic approach to maintaining capacity and standards for biomedical research in the UK. However, it is important to note that the actions set out in the technical notices alone will not mitigate all issues that would arise in the event of a no deal Brexit. While the regulatory measures that the government has put in place to mitigate the impact that leaving the EU without a deal would have, these measures alone will not guarantee continuity of ongoing clinical research in the event of no deal, nor will they necessarily maintain the attractiveness of the UK as a location for future clinical research.

**What further planning or reassurances are required in order to ensure the impact of a no deal Brexit on health and social care would be minimised?**

The UK accounts for 1.7% of clinical research conducted globally. As a result of the additional regulatory burden that will add costs for both industry and government in the UK in the event of a no deal Brexit, ACRO is concerned that the UK would be deprioritised as an early location for clinical research and product launch, delaying patient access to innovative products and offsetting any expected benefits. To mitigate this over the long term, ACRO recommends that the UK should recognise clinical trial approvals granted in other territories, aiming to use the same product dossier and ensure a quick and simple process for industry. ACRO recognises that, given the disparate regulatory regimes and standards (as well as differing medical practices) in place around the world, development of such recognition agreements would be only a long-term solution and require considerable time and extensive resources to ensure equivalence such that the safety of UK patients in the UK is not compromised.

Additional steps that ACRO recommends could be taken by the UK government to increase the attractiveness of the UK for clinical research include the provision of long-term, predictable access to funding and international collaboration for scientific research, improved access to UK patient data, the maintenance and improvement of tax benefits and intellectual property protections to encourage clinical research in UK, and to build on the success of the National Institute for Health Research (NIHR) to continue to establish a more collaborative environment between the NHS and industry to support innovative product use in the clinical trial setting and to modernise the clinical research process. Additionally, the government should ensure that the MHRA is adequately resourced to implement the additional workload that it will be required to take on in the event of a no deal Brexit.

In the immediate term, ACRO welcomes the steps that the UK government is taking with regard to planning for a no deal Brexit. Our concerns relate to the measures that may be put in place by the EU in the event of no deal. Consequently, we consider agreement of the Withdrawal Agreement, to allow the implementation period to come into effect, will be critical in ensuring companies can continue to make all necessary preparations. This should be agreed as soon as possible, recognising the practicalities of the timetable which necessitates Parliamentary

approval in both the UK and the EU to be concluded before March 2019. Alongside the terms of the Withdrawal Agreement, ACRO continues to recommend that regulatory cooperation between the UK and EU is essential to ensure that UK and EU patients continue to have access to novel medicines, medical devices and clinical research, and that the both the UK and EU remain world leaders in life sciences.

Clinical research is a global enterprise in which sponsors 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. In the absence of appropriate agreements between the UK and the EU, there is a danger that ongoing clinical research in both territories will be disrupted, and the overall level of clinical research in the UK reduced, with a significant and serious impact on sponsors, CROs, researchers, patients and the NHS. The life science industry's preferred position, supported by ACRO, is for the UK to maintain continuity with EU regulatory systems, including full participation in EU regulatory processes and alignment of regulations. The industry continues to recommend an overarching regulatory cooperation agreement with the EU in the context of a broader UK/EU special relationship. This should be a long-term, permanent agreement given the complexity, cost and requirement to provide consistent and stable regulation.

ACRO thanks the Health and Social Care Committee for the opportunity to provide comment on this important inquiry and public consultation on the Impact of a no deal Brexit on health and social care. Please do not hesitate to contact ACRO if we can answer any questions at all or provide additional details.

Respectfully submitted,



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