

# Cancer Research UK's policy statement on the future of clinical trials as the UK exits the EU

August 2018

## Summary

Clinical trials are the gold standard for developing evidence to see if a new intervention is safe and effective to become standard practice. They provide patients with opportunities to access innovations at an early stage in their development. Clinical research is a vital strand of Cancer Research UK's (CRUK) work to accelerate progress so that 3 in 4 people survive their cancer for 10 years or more by 2034. We fund nearly 200 clinical trials and recruit around 25,000 patients each year to all trials we support.

The benefits of clinical trials extend beyond the potential benefit to participants, as they contribute to health improvement for broader populations through the provision of better drugs and treatment guidelines. In addition, evidence has shown that NHS Trusts which conduct more clinical research provide better care and have better patient outcomes than those that conduct less clinical research<sup>1</sup>. It is also estimated that clinical research supported by the Clinical Research Network (CRN) has generated £2.4 billion and almost 39,500 jobs<sup>2</sup>.

Europe is a world-leader in the development and running of clinical trials. Over 4,800 UK-EU trials took place between 2004 and 2016<sup>3</sup>. More than a quarter (28%) of trials CRUK fund involve patients from at least one other EU country<sup>4</sup>. Working collaboratively across borders is particularly vital in rare and paediatric cancer research to ensure enough participants.

The UK's departure from the EU has introduced uncertainty to the European clinical trials environment. Of immediate concern is the UK's ability to participate in the future regulatory framework for clinical trials testing new medicines being rolled out in the EU. Action is also needed to ensure: minimal interruption to the supply of trial products; continuation of sufficient collaborative funding initiatives for clinical trials; the ability for researchers to be mobile across borders to support collaborative working; and ability to safely share patient data used in research.

This statement was informed in part by a study commissioned by CRUK, which engaged with researchers, regulators, patients and policy makers from the UK and EU. The resulting report '[Future of clinical trials after Brexit](#)'<sup>5</sup> outlines the short and long-term factors affecting clinical trials in different EU exit scenarios. **Appendix A** provides further background in support of this statement.

## Ensuring an optimal regulatory environment for clinical trials

**The UK and the EU must come to an agreement to ensure the UK can fully participate in the regulatory system created by EU Clinical Trials Regulation (CTR), for the benefit of patients in the UK and the EU.**

- **Building on the commitment to adopt the CTR as far as possible when implemented, the UK Government must now prioritise seeking access to the EU portal and database. The ability for UK-based organisations to act as the Sponsor of clinical trials with EU partners should also be safeguarded, this is key for academic trials.**
- **The European Commission should commit to exploring all possibilities to allow the UK to participate in the CTR system.**
- **UK Government and the European Commission, along with their agencies should provide guidance for researchers conducting clinical trials in preparation for the UK's exit from the EU to ensure there is minimal disruption to trials and patients.**

The CTR<sup>6</sup> will provide a new regulatory framework for the development of new medicinal products across the EU. It will be a major improvement upon the current regulatory system, which is criticised for creating administrative barriers without greater levels of protection to study participants.

Trials involving Investigational Medicinal Products (IMPs) are currently regulated by the EU Clinical Trials Directive (CTD). Different implementation of the CTD in Member States has resulted in a lack of harmonisation and led to several problems (see Table 1, Page 13). The UK's clinical trials community, the Medicines and Healthcare products Regulatory Agency (MHRA), charities and patient groups working in partnership with European collaborators were instrumental in driving welcome changes to the CTD that will be brought in through the CTR<sup>7,8</sup>.

The crucial benefit of the CTR will be a more streamlined approach to approvals through a centralised portal and database, and the reduced divergence in processes across the EU. The UK's ability to fully participate in the system created by the CTR is uncertain as this is subject to negotiations. Participants in our commissioned research highlighted alignment of clinical trials regulation as the highest short-term concern for the future of trials<sup>9</sup>.

If the UK is unable to negotiate access to the underpinning IT infrastructure, one option could be for the UK to adopt the provisions of the CTR in legislation and create a separate but parallel approvals system. Another option is for the UK to set up a bespoke approvals system that does not attempt to mirror the EU portal and database. Either of these scenarios would be damaging and risks creating practical and perceived barriers to collaboration on cross border trials between the UK and EU.

The impact on academic trials is of high concern. Some researchers are already experiencing difficulties collaborating with EU nations. Academic trials are a crucial component of the UK clinical trials landscape. They often trial new combinations of therapies, look at rarer conditions as well as de-risking future investments from industry. After the UK leaves the EU, the ability for UK institutions to lead and sponsor clinical trials involving EU Member States is unclear. UK universities and small companies may not have sites in the EU to act as a legal representative as some countries can require under the CTD or the CTR. Setting up this representative is also likely to be prohibitively expensive or complex.

*"We have had some EU partners... ask if they are better off leading the trial instead of us due to the uncertainty over Brexit. If this continues, it could seriously knock the reputation of UK academics when conducting clinical trials, meaning that UK researchers are not in a strong position to drive or lead research in the future." - a CRUK researcher*

As a matter of urgency, guidance is needed for current and future Sponsors of UK-led pan-EU trials on preparations needed to ensure minimal disruption of current trials. Trials run under the current regulatory system require an EU-based Sponsor or legal representative. Depending on negotiations, an EU Sponsor or legal representative for UK-led trials could be required as early as March 2019.

### **Safeguarding the supply of Investigational Medicinal Products (IMPs)**

**The UK and EU must work together to ensure that trade barriers do not impact the availability or movement of investigational medicinal products (IMPs), clinical trial supplies and medicines after the UK leaves the EU.**

An IMP is any medicinal product which is being tested within a trial or any product, including placebo. This includes newly developed medicines or existing approved medicines. Before IMPs can be released, they must be assessed and certified by a Qualified Person (QP). Currently, 70% of IMPs in ongoing EU trials are QP released from the UK and 30% from the rest of the EU<sup>10</sup>. Many CRUK funded trials are reliant on the movement of IMPs between the UK and EU. Any trade barriers or lack of mutual recognition of QPs between the UK and EU would have severe consequences for

these trials and the patients participating in them. This is particularly true for IMPs with a short shelf life, including radiopharmaceutical products and possibly cell therapy type products.

### Enhancing funding opportunities for clinical trials

**The UK Government should continue to develop long-term funding initiatives for clinical trials. It should also strengthen and develop international collaborations and continue to access funding to support these, including Horizon Europe. Clarity is needed on steps to ensure that the UK can continue to participate and shape the future of such programmes.**

Funding for clinical trials in the UK comes from public, private and charitable sources. Of CRUK's £432 million research spend in 2016/17, £38 million was spent on clinical trials. Our clinical trials also leverage additional funding from industry. The National Institute for Health Research (NIHR) spent £207 million on 263 new research programmes in 2015/16, funding which is hugely valuable to the UK's clinical trials landscape. The NIHR has also invested £36 million over five years for 18 Experimental Cancer Medicine Centres (ECMCs), a vital network that is funded in collaboration with CRUK and the Health Departments of Scotland, Wales and Northern Ireland.

A long-term strategic approach to funding of clinical trials in the UK is necessary to ensure sufficient investment and to drive collaboration. Availability of funding for trials, research and innovation was found by our study participants as the most critical factor impacting on the future of clinical trials to address in the long-term<sup>11</sup>. We welcome commitments from UK Government to increase investment in UK Research & Development (R&D) and to seek to collaborate on future EU research funding initiatives. Whilst there have also been positive announcements from the European Commission regarding the ability for the UK to participate in future EU funding programmes, an agreement has not yet been reached.

### Ensuring a skilled and mobile clinical research workforce

**The UK and EU must continue to co-operate and develop new migration arrangements to ensure the clinical trials workforce can continue to collaborate across Europe. As part of this, the UK must develop an immigration system that enables the UK to attract, recruit and retain global scientific talent at all professional levels regardless of their nationality.**

The successful operation of clinical trials relies on a skilled workforce who can easily collaborate. In 2016, more than half the European Economic Area (EEA) nationals in the UK who answered a CRUK researcher survey had spent time outside the UK for work. A common reason for this travel was scientific collaborations including clinical trials<sup>12</sup>. We welcome acknowledgment from UK Government of the mobility needs of scientists<sup>13</sup>. It is vital that short term mobility can continue to support clinical trial collaborations across Europe. The Home Office should include features of flexibility to enable extensive short- and medium-term movement of the research workforce in the post-Brexit immigration system. This should include cooperating with the EU to develop effective researcher mobility arrangements.

### Protecting the safe sharing of patient data for research

Access to EU data and patient populations is essential for the conduct of clinical and observational trials. In addition, data portability and transparency are critical for ensuring appropriate patient recruitment, a major challenge for clinical trials. For paediatric and rare diseases, the ability to share and access data internationally is vital. In the long term, there is concern in the clinical trials community that lack of harmonisation means UK data is not accepted across Europe or internationally. To avoid negative impacts to the conduct of trials, it is essential for the UK to remain aligned with EU regulation.

## Appendix A – Further information on EU exit and clinical trials

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### 1. Why cross-border clinical trials are important

Clinical trials are the gold standard for developing evidence to see if a new intervention is suitable to become standard practice. They form the basis for deciding whether a new drug or amendment to any existing therapy produces a clinical benefit to patients.

In the field of cancer research, particularly in paediatrics and rare tumour types, the populations are often too small to recruit sufficient numbers onto trials in a single country. In addition, as genomics advances our understanding of disease, researchers are increasingly grouping patients according to the genetic profile of their cancer. This means the pool of eligible patients becomes smaller and one country alone may not have enough patients to make the evidence meaningful. There are also some studies that may start as a single country trial but will need to expand to other countries if recruitment is low and more participants are needed.

The UK is a strong collaborator, supporting the third highest number of pan-EU trials and participating in the most paediatric and rare disease trials<sup>14</sup>. As well as increasing patient populations, collaborating across multiple countries is incredibly valuable to share knowledge and expertise between researchers. In fact, internationally co-authored publications have higher citation scores than those from just one country<sup>15</sup>. Ultimately collaboration improves outcomes for all patients and it is therefore vital that it continues to be encouraged.

#### How we collaborate internationally on trials

The UK is currently conducting nearly 700 oncology trials. 409 (58%) of these trials are also being run in the EU, compared to just 17 (2%) being run internationally outside of the EU<sup>16</sup>. Over 1 in 3 (34%) of CRUK supported clinical trials involve countries outside of the UK. Most of our cross-border trials are with EU nations (28% of our total trials). The current EU Clinical Trial Directive (CTD) means that it is generally simpler than collaborating with nations outside of the EU.

Collaboration on clinical trials with countries outside the EU does happen. In our experience, when collaborating with nations outside of the EU, there is great variation in approval systems, insurance provisions, availability of drugs and clinical differences (including the standard of care) and time zone differences can often produce barriers.

Nicky Gower, operations lead at the UCL Cancer Trials Centre explains “For successful collaboration with countries outside of the EU, it is essential to have good contacts who know the local requirements and to make early contact. This is not possible in every instance.”

### Case Study – The BEACON clinical trial

In 2013, Cancer Research UK scientists and paediatric cancer specialists launched the BEACON-neuroblastoma trial to find the best chemotherapy treatment for children and young adults with recurring neuroblastoma.

Joseph was diagnosed with advanced neuroblastoma when he was just three. Despite undergoing chemotherapy and surgery, he relapsed just before his seventh birthday, which is when his doctor suggested the BEACON trial.

Joseph's mum Sarah said "We were glad to take part in the BEACON study and understand that the trial was made possible by international collaboration. Treatment options can be very limited for children like Joseph and, as a family, it is amazing to know that scientists are working together across Europe on treatments. We welcome all research that can help find cures and kinder treatments to fight cancer – when treatment options run out, the lives of children like Joseph are dependent on the innovation that this collaboration can bring."

The rarity of recurrent neuroblastoma and therefore low number of patients means that the BEACON-Neuroblastoma trial could not have happened in a single European country. It's this type of clinical trial which Cancer Research UK wants the UK to continue to play a globally significant role in. This international collaboration is crucial for us to make progress for patients, especially for children and adults with rare cancers.

### Ensuring an optimal regulatory environment for clinical trials

New medicines that are being tested in a clinical trial are termed Investigational Medicinal Products (IMPs). Trials involving IMPs are currently regulated by the Clinical Trials Directive (CTD). The CTD is implemented in Member States through national legislation. This includes a system in which a single regulatory body within each of the Member States acts as a National Competent Authority (NCA). Currently, in the UK this requires two approvals from both the National Competent Authority (the MHRA) and Ethics Committees (via the HRA). For cross-border trials, individual assessments are conducted by each Member State, independent from all other Member States.

The CTD was the first step in harmonising clinical trials throughout the EU. However, full harmonisation was not achieved and the original aims of the CTD were not met. The lack of harmonisation stems from the different implementation of the CTD through national legislation, which has resulted in divergence and led to the problems described in Table 1 (page 13). CRUK, alongside the UK's clinical trials community, patient lobby groups and the MHRA working in partnership with European collaborators were instrumental in driving welcome changes to the CTD that will be brought in through the CTR<sup>17,18</sup>.

#### i. The benefits of the CTR

We believe the CTR will be a major improvement upon the current CTD, criticised for creating administrative barriers without greater levels of protection to study participants. Some of the benefits the CTR will bring include:

##### ***A centralised portal and database***

The new approval process will take place through the new EU portal online software, including submission, co-ordinated assessment and communication between Sponsors and participating countries. This will simplify the application and approval procedures and decrease the administrative burden for clinical trials. The centralised procedure will be vital to speeding up setup and monitoring of trials, including providing safety updates.

The portal and database will differ from the existing EudraCT, which has information about clinical trials of IMPs with at least one site in the EU. Currently under the CTD, Sponsors do not have direct access to the database and information must be passed through the NCA, making the process longer and more bureaucratic. The CTR will give Sponsors direct access to a new database with all of the information about trials, including start date, end date and results.

#### ***A single co-ordinated approval process***

Simplified application and approval procedures will decrease administrative burden for clinical trials. By centralising decisions that apply equally to all Member States, individual countries only need to assess specific elements that relate to their own situation. This will speed up the process and reduce duplication of effort in cross-border trials. A single participating country will be designated the Reporting Member State (RMS) for the purposes of the trial. The RMS will provide the initial assessment of the trial ('Part I approval'). This assessment is like MHRA approval, but under the new system the approval will apply uniformly to all Member States. Each participating country will still need to perform assessments for ethical requirement ('Part II approval') as these differ at the national level. The same procedure will apply to substantial amendments made to the trial.

#### ***Improved approach to patient safety and transparency***

A safety reporting database will be linked to the portal and database. This will provide a simplified reporting system for capturing suspected unexpected serious adverse reactions (SUSARs) that will be less burdensome. The database will also include extensive information on clinical trials, from authorisation to the trial summary results of all trials authorised in the EU/EEA under the CTR. There is agreement between Member States to work together on safety assessment. In addition, safety assessment Member States (saMS) will be selected. This will enhance and speed up the sharing of information of procedures within trials that could be compromising patient safety, preventing safety issues with additional patients.

#### ***Co-sponsorship***

The CTR will allow for all NCAs to recognise co-sponsorship and will therefore not reject trials in which co-sponsorship occurs as currently happens under the CTD. Co-sponsorship is a concept unique to the UK and, in particular, to academic trials where universities and hospitals share responsibility. Sharing responsibility allows institutions and organisations that are not completely capable of taking on full liability of sponsoring a trial to participate and share responsibility with others. There have been cases under the CTD where UK trials have attempted to expand into another EU Member State and had their applications rejected by the NCA because co-sponsorship was a division of Sponsor responsibilities, despite the UK's NCA (the MHRA) accepting this arrangement.

#### ***Reduced divergence between Member States***

As it is a Regulation, rather than a Directive, the CTR will be applied more consistently across all Member States, giving trial Sponsors a more standard approach to conducting clinical trials. There is currently divergence to how the CTD is applied to national laws as it is open to interpretation and subject to more national requirements. This results in substantial delays in opening trials involving multiple countries. These delays will be reduced by the harmonised approach of the CTR.

#### ***Adoption of a more risk proportionate approach***

The CTR takes into consideration, and provides further clarity on, a more proportionate risk-based approach to trial authorisation and management. This builds on a more risk-proportionate approach across the EU, introduced by the MHRA. This will help to reduce unnecessary administrative burden for low risk trials. A trial using an IMP that works within its existing Marketing Authorisation would

be subject to a more proportionate level of regulation. This is of high priority to CRUK as we support academic research that investigates how to optimise the use of medicines that already have a marketing authorisation; for example, the IBIS-II trial comparing an off-patent drug, Anastrozole with Tamoxifen in breast cancer patients. The CTR allows the protocol to include a list of known side-effects of the IMPs which will result in less safety reporting of these side-effects, minimising administrative burden.

### ***Ambitious timelines and a flexible appraisal system***

The CTR sets ambitious timelines for review and has a flexible appraisal system. There are also no minimum timelines prescribed which adds the potential for reviews to be even quicker. During the appraisal of substantial amendments, a flexible system is helpful as it means additional information can be requested from the Sponsor. The number of amendments is increasing as adaptive trials – trials that enable continual modification to the trial design based on interim data analysis<sup>19</sup> – become increasingly common. Additional information cannot be requested under the CTD, resulting in substantial delays as amendments are rejected by the NCA when assessors have insufficient information. Despite improvements to the approvals process being introduced by the MHRA, this is an issue for many trials, including UK-only trials. Under the CTR, these rejections will not occur, and the additional information provided by the Sponsor should minimise disruption.

#### **ii. The current situation**

Due to delays in the establishment of the EU portal and database, the CTR will be applied after the UK exits the EU. This means that implementation of the CTR in the UK will no longer be automatically captured by the EU (Withdrawal) Bill<sup>20</sup>. UK Government has committed to aligning as closely as possible with the CTR, including adopting all the relevant legislation<sup>21</sup>. However, alignment does not provide the same advantages as full participation in the EU CTR system. It does not guarantee access to the centralised CTR portal and database, nor allow for UK organisations to act as Sponsors for trials without the added need for an EU-based legal representative.

Like many factors, these will require negotiation as part of the future UK-EU relationship. Any delay in fully aligning with the CTR could leave the UK behind, without access to a harmonised regulatory system. It is crucial that an agreement is made before the CTR is implemented. Our report *Future of clinical trials after Brexit* outlines the possible levels of alignment and their implications<sup>22</sup>.

#### **Summary of levels of alignment with the CTR:**

- **Full alignment** – a bespoke agreement is agreed between the UK and EU to allow the UK to participate fully in the provisions of the CTR and to access the portal and database
- **Partial alignment** – the UK implements the provisions and processes in the CTR as far as possible but is unable to access the portal and database
- **No alignment** – the UK does not implement the provisions of the CTR and keeps existing clinical trials legislation in place. The UK may choose to adopt a bespoke regulatory system or align with an alternative market

#### **iii. What if access to the portal and database is not possible?**

If the UK is unable to negotiate access to the portal and database associated with the CTR, one option would be for the UK to implement a parallel system. In this case, the full advantages available to the rest of the EU through the CTR would not extend to the UK as the benefit of a single approval process would be lost. This could cause inefficiencies meaning longer approval times for cross-border UK-EU trials. Therefore, the UK risks becoming a less attractive place to conduct trials.

It is our understanding that the MHRA and HRA are taking steps to prepare for this eventuality by planning a parallel system. Although there is currently limited detail on the parallel system, we

understand that it would require a similar dossier and timeline to the CTR's and there are plans for the two systems to communicate to ensure alignment on approvals. To ensure smooth interaction and minimise any burden of multi-country trials there should be ongoing dialogue between the EMA and the relevant UK bodies.

Another option would be for the UK to set up a bespoke approvals system that does not aim to mirror the portal and database associated with the CTR. There is a greater risk of the UK becoming a less attractive destination for clinical trials with this scenario. A bespoke UK system could lead to additional burden as multiple submissions would be required for trials with sites both in the UK and other EU countries. The system could also take time and cost money to implement.

Both these scenarios risk damaging the UK's future research prospects by creating practical and perceived barriers to collaboration on cross border clinical trials. UK Government will need to mitigate against this perception and encourage collaboration. This can be achieved by providing reassurance and guidance to researchers and through working closely with EU stakeholders.

#### **iv. The impact of not adopting the CTR on different types of trials**

There are many types of clinical trials involving medical products. They come in a variety of designs, are conducted by different types of organisations, on different disease types with a diversity of population demographics and with sites located in different jurisdictions. These trial types will be impacted by the inability to fully align with the CTR:

##### ***Academic trials***

The ability for the UK to lead and sponsor future clinical trials with EU Member States is not clear. The CTR states that if a Sponsor is based outside the EU, either a legal representative or a contact person must be established within the EU, subject to specific requirements of the collaborating Member State(s)<sup>23</sup>. CRUK supports trials through a range of mechanisms including through the provision of core funding to eight of our own Clinical Trials Units (CTUs). These CTUs are based within universities, who act as Sponsors of clinical trials. Universities are unlikely to have a legal person in another EU nation to act as a legal representative and the cost of setting up this representative may also be prohibitively expensive or complex. Under the CTR, the legal representative will have more responsibility than under the CTD, including ensuring compliance with

##### **Case study – University of Birmingham: CRUK Clinical Trials Unit (CRCTU)**

The CRCTU is one of the largest cancer trials units in the UK and has been in existence for more than 40 years. The CRCTU specialises in the design, conduct and analysis of cancer clinical trials for Investigators nationwide and internationally in a number of specialist areas, including paediatric cancer.

With such a large international portfolio, the CRCTU relies on efficient collaboration between the UK and EU nations. At least 8 international trials sponsored by the University of Birmingham and led by CRCTU will still be running after the UK leaves the EU (including after the end of the transition period) and are likely to be impacted by the regulatory changes to clinical trials.

Professor Pamela Kearns, Director of the CRCTU and Paediatric Oncologist at Birmingham Children's Hospital, understands the difficulties lying ahead for UK academic clinical researchers if the UK cannot participate and therefore does not have access to the digital infrastructure associated with the CTR, stating " When we are no longer an EU member, the major impact on our European trial collaborations will be the additional legal hurdles to comply with EU trials laws and our inability to participate in new harmonised approval processes, which will add cost, complexity and delays to UK's participation in European collaborations and could act as a disincentive to work with UK partners."

the Sponsor's obligations and being an addressee for all communications with the Sponsor. Around 40% of all UK oncology clinical trials are non-commercial and therefore may experience the same issues if the UK is not able to fully participate in the CTR regulatory framework<sup>24</sup>

### ***Paediatric and rare disease trials***

Although each rare tumour type has a small population, when taken together rare cancers make up over 20% of all cancer diagnoses worldwide<sup>25</sup>. Cross-border collaboration on trials is critical for these types of trials involving paediatric and rare cancers. This is because the patient populations in individual countries are often too small to recruit sufficient numbers onto trials and to make the evidence meaningful. To get sufficient clinical trial data to inform interventions, a larger pool of patients is required, which is sometimes only available if multiple countries are involved. There are also some studies that may start as a single country trial but will need to expand to other countries if recruitment is low and more participants are needed. Full participation in the CTR system will be particularly important for these types of trials. Currently, CRUK has 44 active clinical trials involving IMPs with another EU nation, many of which are for rare and paediatric cancers.

### ***Stratified trials***

As more trials move towards a more personalised approach, we will be grouping patients according to the genetic profiles of their tumours. These trials have the potential to bring greater benefits to patients through more targeted treatments. However, the population numbers for testing some drugs will become smaller and therefore cross-border collaboration will become increasingly important to ensure enough patients are on the trial. Phase II and III trials will be especially affected, as these studies require a greater number of patients than earlier phase studies. Of CRUK's active trials, 88% are phase II and III trials.

### ***UK-only trials***

The main benefit of the CTR will be faster and more consistent decisions on cross-border EU clinical trials, increasingly important to our trials. Although the initial CTR implementation period may lead to slight delays due to teething problems, the longer-term benefits to all trials, will include simplified and more flexible approvals and notifications due to the centralised procedures. Our commissioned study showed that operating under a separate UK system from the CTR could potentially simplify and speed up processes for some UK-only studies, particularly for new trial designs<sup>26</sup>. However, the CTR does not prescribe minimum timelines and introduces a more flexible appraisal system which could also improve timelines for innovative UK-only trials. If adoption of the CTR is not achieved, our study participants indicated UK-only innovative trials as the most likely area where the UK could attempt to focus on building competitiveness<sup>27</sup>.

Ultimately, for future collaboration between the UK and EU in cross-border trials, full alignment with the CTR is vital. Diverging would mean additional complexity, delays to set-up and completion, and risks the UK's ability to lead these trials.

**The UK and the EU must come to an agreement to ensure the UK can fully participate in the regulatory system created by EU Clinical Trials Regulation (CTR), for the benefit of patients in the UK and the EU.**

- **Building on the commitment to adopt the CTR as far as possible when implemented, the UK Government must now prioritise seeking access to the EU portal and database. The ability for UK-based organisations to act as the Sponsor of clinical trials with EU partners should also be safeguarded, this is key for academic trials.**
- **The European Commission should commit to exploring all possibilities to allow the UK to participate in the CTR system.**

## Guidance for researchers

Findings from our *Future of clinical trials after Brexit* report reflect the feelings of researchers and other members of the clinical trials community<sup>28</sup>. One prominent view is that UK Government could better communicate on their preparations for alternative outcomes. Guidance on preparedness is crucial for researchers to continue conducting clinical trials with minimal disruption.

One area of guidance needed is on the preparations current and future Sponsors of UK-led pan-EU trials need to make to ensure minimal disruption of these trials. This is particularly time sensitive for trials run under the Directive in a 'no deal' scenario. It is our understanding that in this scenario an EU-based Sponsor would need to be secured by March 2019 to avoid possible halting of these trials.

**UK Government and the European Commission, along with their agencies should provide guidance for researchers conducting clinical trials in preparation for the UK's exit from the EU to ensure there is minimal disruption to trials and patients.**

### 2. Safeguarding the supply of Investigational Medicinal Products (IMPs)

An IMP is any medicinal product which is being tested within a trial or any product, including placebo, used as a reference in a clinical trial. This includes products already holding a marketing authorisation and being used in a different form or for a different purpose. Currently, CRUK has 44 active clinical trials involving Investigational Medicinal Products (IMPs) with another EU nation, many of which are for rare and paediatric cancers.

Before IMPs can be released, they must be assessed and certified by a Qualified Person (QP). The QP must ensure that the IMP has been manufactured in accordance with Good Manufacturing Practice (GMP) as set out by EU regulation. IMPs that are manufactured and/or certified in the EU can move freely between Member States without the need for further QP inspection. When the UK leaves the EU, it is not clear if a UK certified QP will still be recognised for IMP distribution in the EU. If there are no specific agreements relating to the import and export of goods, there could be delays impacting both UK and EU trials sites. An IMP used in a UK trial site that is manufactured and QP released in the EU will have to be imported and potentially retested. An IMP used in an EU trial site that is manufactured and tested in the UK could also be subject to delays and duplicate testing.

Currently, 70% of IMPs in ongoing EU trials are QP released from the UK, meaning that 30% are from the rest of the EU<sup>29</sup>. Any delay in accessing IMPs will negatively impact the timelines of clinical trials and therefore delay the benefits reaching patients.

CRUK's Centre for Drug Development (CDD) is currently running two trials where the IMP has been imported into another EU Member State before being transferred into the UK. There is also a trial where the IMP is manufactured in the UK but QP released in Sweden, and another trial where the IMP will be manufactured in Italy. It is vital there are no delays in the access to these IMPs. Depending on what happens with the Customs Union, importation of IMPs, Active Pharmaceutical Ingredients (API) and other materials used in the manufacture of IMPs could be impacted by increased costs and delays at customs.

Delays in the import and export processes will have larger impacts on IMPs with a short shelf life, including radiopharmaceutical products and possibly cell therapy type products such as CAR T-cell therapy. This would not only delay patients from accessing potentially innovative therapies but would also delay any beneficial interventions identified in trials from reaching further patients.

Currently, mutual recognition agreements exist between the EU and third countries, such as Canada, that allows for IMPs imported from sites in these countries to be more readily accepted by the importing EU QP. This is thanks to the acceptance of the GMP standards as equivalent and

acceptable to each other. When the UK leaves the EU, the UK may have to renegotiate similar terms, which will take time and incur costs.

#### **Case Study: Neuroblastoma trial**

A CRUK trial at our Centre for Drug Development involved the manufacture of an IMP, the radioactive imaging agent <sup>124</sup>I-mIBG. The IMP is manufactured on a per patient basis in Manchester and must be administered within 24 hours of production. The manufacturer buys the Iodine-124 from a facility in the Netherlands and with a half-life of 4.2 days, any delays to import could mean that the batch can't be manufactured due to the radioactive yield being too low. This could seriously impact the patient and the trial.

**The UK and EU must work together to ensure that trade barriers do not impact the availability or movement of investigational medicinal products (IMPs), clinical trial supplies and medicines after the UK leaves the EU.**

### **3. Enhancing funding opportunities for clinical trials**

Funding for clinical trials in the UK comes from public, private and charitable sources. Of CRUK's £432 million research spend in 2016/17, £38 million was spent on clinical trials. Our clinical trials also leverage additional funding from industry. The National Institute for Health Research (NIHR) spent £207 million on 263 new research programmes in 2015/16, funding which is hugely valuable to the UK's clinical trials landscape. The NIHR has also invested £36 million over five years for 18 Experimental Cancer Medicine Centres (ECMCs), a vital network that is funded in collaboration with CRUK and the Health Departments of Scotland, Wales and Northern Ireland.

To fully benefit from this investment, a long-term strategic approach to funding clinical trials in the UK is needed. This would ensure sufficient future investment and drive future collaboration. Availability of funding for trials, research and innovation was found by our study participants as the most critical factor impacting on the future of clinical trials to address in the long-term<sup>30</sup>. We welcome the commitment from UK Government to increase investment in UK R&D to 2.4% of GDP by 2027. With the UK's departure from the EU, it is vital that the process for this is outlined and implemented at pace and includes support for clinical research.

We also welcome the UK Government's intention to collaborate on future EU research funding initiatives in exchange for maintenance of excellence and sufficient influence, and to seek a "cooperative accord" on science and innovation<sup>31 32</sup>. The current framework programme, Horizon 2020, supports the clinical trials ecosystem through schemes like the Innovative medicines Initiative<sup>33</sup>. Plans for the next EU framework programme, Horizon Europe, indicate an openness for the UK to fully associate<sup>34 35</sup>. However, an agreement is not yet reached, and clarity is needed on the steps to ensure that the UK can continue to participate and shape the future of such programmes.

**The UK Government should continue to develop long-term funding initiatives for clinical trials. It should also strengthen and develop international collaborations and continue to access funding to support these, including Horizon Europe. Clarity is needed on steps to ensure that the UK can continue to participate and shape the future of such programmes.**

### **4. Ensuring a skilled and mobile research workforce**

The successful operation of clinical trials relies on a skilled workforce and for cross-border trials to run smoothly the movement of the workforce to share data, equipment, knowledge and expertise is integral. It is therefore vital that the UK and EU continue to co-operate and develop new migration arrangements to ensure a highly skilled and mobile clinical trials workforce.

Nearly 50% of all UK cancer research involves international collaboration<sup>36</sup>. In 2016, more than half the EEA nationals in the UK who answered a CRUK researcher survey had spent time outside the UK

for work. Some of these were short trips whereas some lasted a few months to a year<sup>37</sup>. Common reasons for this travel were: collaborations (such as clinical trials), giving and receiving training, use of equipment, verifying data, sharing knowledge, attending conferences, and to work in fixed-term/short-term contracts. It is vital that this type of short term mobility can continue to support clinical trial collaborations across Europe. We welcome UK Government acknowledgment of the mobility needs of scientists. The Home Office should include features of flexibility to enable extensive short- and medium-term movement of the research workforce in the post-Brexit immigration system. This includes cooperating with the EU to develop effective researcher mobility arrangements.

#### **Case Study – ENGOT and the importance of researcher mobility to clinical trials**

The European Network for Gynaecological Oncological Trials (ENGOT) is an international network consisting of 20 trial groups including researchers from 25 European countries. The network coordinates and promotes pan-European clinical trials in order to bring the best treatment to gynaecological cancer patients and enable access to clinical trials for every patient in Europe.

Vital research on rare cancers, like the clinical trials coordinated by ENGOT, must often be carried out in several different countries to ensure enough patients are recruited within a given timeframe to robustly answer the research question. By developing a network of collaborators and opening a trial across many nations, recruitment is thus accelerated. The trial can be run more effectively and efficiently so that new clinical treatments can be assessed sooner and brought to market earlier.

Throughout the process, researchers must travel in order to set up trials in different countries, monitor trial data at individual sites and close studies. Furthermore, clinical researchers attend conferences and meetings in Europe, to ensure they are up to date with the current evidence for treatments, enable networking and collaboration, and to participate in scientific debates on new trials.

According to Laura Farrelly, Trials Group Lead at UCL and newly elected (taking office in April 2018) Administrative Chair of ENGOT, if visas were required for UK researchers to conduct all of these crucial activities in the EU, this would delay travel plans and increase costs. Travel within Europe may even become prohibitive for some researchers, depending on whether their employer is able to accommodate the expense. If this were the case, Laura says “conducting clinical trials with our European colleagues would become more difficult, and the UK could not be as involved in collaborative trials or networks”.

**The UK and EU must continue to co-operate and develop new migration arrangements to ensure the clinical trials workforce can continue to collaborate across Europe. As part of this, the UK must develop an immigration system that enables the UK to attract, recruit and retain global scientific talent at all professional levels regardless of their nationality.**

#### **5. Protecting the safe sharing of patient data for research**

Access to EU data and patient populations is essential for the conduct of clinical and observational trials. In addition, data portability and transparency is critical for ensuring appropriate patient recruitment, a major challenge for clinical trials. For paediatric and rare diseases, the ability to share and access data internationally is vital. In the long term, there is some concern in the clinical trials community that a lack of harmonisation might mean that UK data is not accepted across Europe or internationally. It is essential for the UK to remain aligned with EU regulation. Without alignment, the UK would experience increased bureaucracy and costs, or even prevent data from being shared across borders, negatively impacting the conduct of trials.

**Table 1:** Table summarising the issues reported with Clinical Trial Directive (CTD) and how the CTR will address these issues

<b>Issue with CTD</b>	<b>Problem caused</b>	<b>How CTR will remedy</b>
<b>Interpretation:</b> Directive allows for different interpretation and implementation by MS	<b>Variation in implementation</b> throughout MS, causing increased bureaucracy and leading to longer set-up times and increased cost	<b>Regulation</b> will result in less variation in interpretation, and implementation will not differ between MS
<b>Separate approvals:</b> Each MS is required to submit multiple applications to respective regulators individually through different means	<b>Delays and increased bureaucracy</b> associated with the multiple applications	<b>A simplified and streamlined regulatory process:</b> The Sponsor will submit an electronic application which is coordinated through one single access point in the portal by the RMS. Each MS will be make a decision separately but will be coordinated resulting in a harmonised process
<b>No risk proportionality:</b> No differentiation between lower risk trials and other trials	<b>Over-regulation</b> due to the 'one size fits all' approach	<b>Adoption of a more risk-proportionate approach,</b> including the addition of a category for low-intervention trials
<b>Unclear definition of IMPs:</b> The lack of clearly defined IMPs results in inconsistent application across MSs	<b>Divergent assessment outcomes,</b> some MS regulators classifying licensed drugs involved in trials as IMPs even if they are being used for their existing indication, while others are not	The co-ordinated assessment of Part 1 application where IMPs will be defined so should be agreed approach between MS's in trial
<b>Rigid appraisal system:</b> No flexibility in trial setup procedure	<b>Applications are being rejected</b> when regulators needed to request more information	<b>Introduction of a flexible appraisal system</b> that allows for regulators to request more information
<b>Lack of clarity of what constitutes a substantial amendment:</b> Uncertainty over whether or not to submit amendments and no timelines associated with substantial amendments	<b>Over-reporting and extra bureaucracy</b> for researchers and regulators and halting trials while amendments are reviewed	<b>Substantial modifications</b> will have timelines associated with their review (shorter than the initial authorisation of the trial). The UK championed this as it was already in national legislation
<b>Safety reporting:</b> Suspected unexpected serious adverse reactions (SUSARs) reporting takes up to two days for each event due to the amount of information requested	<b>SUSAR reporting is burdensome</b> for trials involving licensed drugs where undesirable effects on the label does not reflect what is commonly observed in routine clinical practice. This leads to known common side effects being reported as SUSARs	<b>A safety reporting database will be linked to the portal and database</b> will provide a simplified reporting system for SUSARs that will be less burdensome
<b>Trial sponsorship:</b> Every trial requires a nominated Sponsor. Currently in most Member States, only a single Sponsor is used	<b>Some NCAs only allow one Sponsor to assume all responsibility</b> for reporting progress, causing rejection of some UK trials with multiple Sponsors	<b>Introduction of the concept of co-sponsorship</b> for clinical trials will share regulatory responsibility for the entire clinical trial

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