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Cancer Research UK's policy statement on alignment with the EU Clinical Trial Regulation

Clinical studies are the gold standard for developing evidence to see if a new intervention is suitable to become standard practice. They also 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 over 200 clinical trials and recruit around 25,000 patients each year to all trials we support.

Europe is a world-leader in the development and running of clinical trials. The UK plays an integral role in this landscape as a leader and collaborator in thousands of trials. Over 4,800 UK-EU trials took place between 2004 and 2016[1]. More than a quarter (28%) of CRUK's trials involve patients from at least one other EU country[2]. Working collaboratively across borders is particularly vital in rare and paediatric cancer research to ensure enough participants.

CRUK's priority as the UK exits the EU is to safeguard the interests of patients and research. Regulatory alignment for drugs licensing and clinical trials is critical to achieving this. CRUK played a major role in the development of the forthcoming EU Clinical Trial Regulation[3] (EU CTR). We believe the EU CTR is a positive step forward in the regulation of clinical trials of potential medicines. For example, it will harmonise the assessment and supervision process for clinical trials via a central EU portal and database, currently being set up by the European Medicines Agency (EMA).

As the UK exits the EU, it's vital the ability to run trials and collaborate across the EU is maintained. Implementation of the EU CTR has been delayed until after March 2019 and will therefore not be captured in the EU (Withdrawal) Bill. Urgent clarification is needed on the status of this regulation. This paper sets out CRUK's position on alignment with the EU CTR (a separate policy statement on drug licensing can be seen on our website).

Recommendations

The UK and the EU must come to an agreement to ensure the UK can adopt and align with the EU Clinical Trials Regulation, for the benefit of patients in the UK and the EU.

To achieve this:

- **UK Government must prioritise alignment with the EU CTR during negotiations on our future relationship with the EU and commit to adopting the EU CTR when implemented. It is particularly important that the UK Government seeks access to the EU portal and database, and the ability for UK-based organisations to act as the Sponsor of clinical trials which include EU partner countries.**
- **The EU Commission and the EMA should commit to exploring all possibilities to allow the UK to participate in the EU CTR system.**

The current situation

Due to delays in the establishment of the EU portal and database, the EU CTR will be applied in late 2019 instead of 2018[4]. This means that implementation of the EU CTR in the UK will no longer be automatically captured by the EU (Withdrawal) Bill[5]. Therefore, the process of the UK adopting the legislation is uncertain. Like many others, alignment with the EU CTR will be an issue that requires negotiation as part of the future relationship between the UK and EU. Any delay in aligning with the

EU CTR could leave the UK behind, without access to a harmonised regulatory system. It is crucial that an agreement is made before the EU CTR is implemented.

We welcome UK Government plans to seek regulatory alignment with the EU to protect public health and safety[6]. We support the ambition to put patients at the heart of regulation, provide long-term stability and ensure the UK is a leader in medical innovation. We would welcome a similar commitment from the EU.

Achieving UK alignment with the CTR

Our preferred scenario is that **the UK and the EU come to an agreement that allows the UK to fully participate in the EU CTR system.** This scenario is vital for close collaboration on cross-border clinical trials to continue and for the UK to easily lead pan-EU trials**.**

Although the future is uncertain, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) has begun working on drafting the secondary legislation required to implement the EU CTR. We strongly support the MHRA's aim to achieve a deal for UK participation in the EU CTR system. However, it's clear that further work is needed to understand how this can be achieved in practice.

Our understanding is that the Regulation includes certain stipulations where it is not clear if the UK will be able to participate when it is no longer part of the EU. Priority examples include:

The EU portal and database: it is not entirely clear whether the UK, as a non-member state, will be able to connect into the EU CTR single submission and access the portal and database. Access to the portal and database is not currently granted to third countries.

Trial leadership: Collaboration in cross-border trials is vital in many cases, and the UK's ability to lead pan-EU trials is at risk. The EU CTR includes a mechanism for UK researchers to participate in and co-sponsor a clinical trial with an EU partner[7]. However, it requires non-EU sponsors, which the UK will become, to have a legal representative within an EU member state. This will significantly restrict the ability of academics based in UK institutions to lead pan-EU trials. The worst case scenario here is that some pan-EU trials wouldn't be taken forward as a result.

Case study: Pan-EU pancreatic cancer trial (Cancer Research UK funded)

Pancreatic cancer is one of the hardest cancers to treat, and has one of the lowest survival rates. The European Study Group for Pancreatic Cancer (ESPAC) wants to change this. ESPAC formed in 1989, and their research has contributed to accelerated improvements in survival and quality of life for patients. Since the 1980s, short term survival has increased by around 60%.

But ESPAC know there is more to do. Just 1% of people diagnosed with pancreatic cancer in England and Wales survive for ten years or more. In the UK in 2014 alone, there were around 9,400 new cases of pancreatic cancer, and 8,800 deaths.

In 2008, they set up the ESPAC-4 clinical trial. By 2014, it had recruited 732 patients from the UK, Germany, Sweden, and France. Around half of trial participants received an innovative combination of chemotherapy drugs. The other half received the standard chemotherapy treatment.

An extra 13% of patients on the trial lived for five years when given the combination of chemotherapy drugs. This brings five year survival to almost a third, a huge result for patients.

ESPAC is led in the UK by a team at Liverpool University and includes experts from all over Europe.

Running trials for rarer cancers across the EU means we can develop new treatments that benefit patients in UK and across the world. Groups like ESPAC need to be able to continue their life-saving work, in the immediate and longer term post-Brexit environment.

Should we be thinking differently?

Ultimately, for the UK to collaborate effectively with the EU in cross-border trials, alignment with the EU CTR is essential. Diverging in any way for these types of trials would lead to additional complexity, delays to set-up and completion, and risks the UK's ability to lead these trials. Given these trials tend to be for rarer and paediatric cancers, any delays would be unacceptable for patients across Europe. However, for some UK-only studies there may be options for simplified processes in addition to alignment on cross-border studies. While every option should be explored, this must not be at the expense of the ability to collaborate in multi-state trials.

Background

Cross-border clinical trials benefit UK and EU patients

Clinical studies are vital to test whether novel interventions improve outcomes for cancer 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. Although each rare tumour type has a small population, when taken together rare cancers make up over 20% of all cancer diagnoses worldwide[8].

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[9]. As well as increasing patient populations, collaborating across multiple countries is incredibly valuable to share knowledge and expertise between researchers. Ultimately this collaboration improves outcomes for all patients.

Clinical trials in cancer are also evolving. Increasingly researchers are stratifying patients according to the genetic profile of their cancer. For some trials, the pool of eligible patients therefore becomes smaller and one country alone may not have enough patients to make the evidence meaningful. Therefore, to get sufficient clinical trial data to inform interventions, a larger pool of patients is required. 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 EU CTR is a positive step forward in the regulation of clinical research

We believe the EU CTR will be a major improvement upon the current Clinical Trials Directive (CTD), criticised for creating administrative barriers without greater levels of protection to study participants. CRUK, alongside the UK's clinical trials community, patient lobby groups and the MHRA were instrumental in driving these welcome changes brought in through the EU CTR[10,11]. We identified that the CTD was not achieving its aims, produced key evidence and called for it to be revised. We then fed in during the development of the EU CTR to ensure the final version would best support research. The changes driven forward by the UK-based research community and organisations will bring benefits to clinical research and patients across Europe.

Some of the benefits the EU CTR will bring include:

A single co-ordinated approval process and portal

Simplified application and approval procedures will decrease the administrative burden for clinical trials and support transparency. The entire process will take place through the new EU portal and database online software, including submission, co-ordinated assessment and communication between Sponsors and participating countries.

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 multi-country 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 similar to 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.

Reduced divergence between member states

As it is a Regulation, rather than a Directive, the EU 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 EU CTR.

Adoption of a more risk proportionate approach

The EU 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 Investigational Medicinal Product (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 often fund academic research that investigates how to optimise the use of medicines that already have a marketing authorisation. The EU CTR allows the protocol to include a list of known side-effects of the IMP(s). The safety reporting of these known side-effects is reduced, minimising administrative burden.

Quicker trial timelines

The EU CTR sets ambitious timelines for review and has a flexible appraisal system. During the appraisal of substantial amendments, additional information can be requested from the Sponsor. Additional information cannot be requested under the CTD, resulting in substantial delays as amendments are rejected by the MHRA when assessors have insufficient information. The additional flexibility in the EU CTR will address this issue.

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[1] The impact of collaboration: The value of UK medical research to EU science and health (2017) http://www.cancerresearchuk.org/about-us/we-develop-policy/we-work-with-government/exiting-the-eu/uk-and-eu-research

[2] Statistics from CRUK's internal databases and include clinical trials from our Clinical Research Committee, New Agents Committee and Centre for Drug Development.

[3] Regulation (EU) No 536/2014 of the European Parliament and of the Council of of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

[4] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp

[5] Letter from Robin Walker (DExEU) to Norman Lamb (Chair of Commons Science and Technology Select Committee) (September 2017) http://www.parliament.uk/documents/commons-committees/science-technology/170921-Robin-Walker-to-Norman-Lamb-DExEU%20letter.pdf

[6] The UK wants to continue to work with the EU on medicines, Jeremy Hunt and Greg Clark joint letter, Financial Times (July, 2017) https://www.ft.com/content/a94326ac-5dbd-11e7-9bc8-8055f264aa8b?mhq5j=e5

[7] Article 74, Clinical Trial Regulation (EU Regulation No 536/2014) https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

[8] Gatta, G., van der Zwan, J.M., Casali, P.G., Siesling, S., Dei Tos, A.P., Kunkler, I., Otter, R., Licitra, L., Mallone, S., Tavilla, A., Trama, A., Capocaccia, R., RARECARE working group. *Rare cancers are not so rare: the rare cancer burden in Europe.* Eur J Cancer, 2011. **47**(17): 2493-511 https://www.ncbi.nlm.nih.gov/pubmed/22033323

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[10] Reforming the European Clinical Trial Directive (2011) http://blogs.bmj.com/bmj/2011/09/26/peter-johnson-reforming-the-european-clinical-trials-directive/

[11] Proposal for an EU Regulation on Clinical Trials, a joint statement from non-commercial and commercial organisations http://www.cancerresearchuk.org/sites/default/files/joint_statement_on_the_commissions_proposals_for_the_clinical_trials_regulation.pdf