

The impact of Brexit: Patient access to medical research

Patients will suffer unless there is a new partnership on science and research between the EU and the UK after Brexit. The Brexit Health Alliance believes that patients across the European Union, including the UK, currently benefit enormously from the current close collaboration between medical researchers who investigate, develop and test new treatments on an EU-wide basis. The Alliance has highlighted three areas of uncertainty for the medical research community:¹

1. Will the UK be able to participate fully and receive/contribute funding from EU programmes and collaborative opportunities to advance the discovery and understanding of diseases and ill-health across Europe?
2. Will those involved in medical research, including healthcare professionals, technicians and patients, be able to travel and work across the EU as freely as they do now?
3. Will patients across Europe and the UK continue to benefit from pan-European clinical trials which involve the UK? Will UK patients be able to benefit as quickly from new drugs and treatments if the UK is not fully aligned with EU rules regulating medical research, medicines and medical devices?

This briefing sets out how patients across Europe have benefited from pan-European collaboration on medical research. It outlines what is at stake if this collaboration is set back and how UK and EU decision-makers can mitigate the risks.

What the Brexit Health Alliance is calling for:

- A positive future cooperation model for research and innovation between the UK and the EU, which includes UK involvement in EU-funding programmes and which supports health research, innovation networks and clinical trials.
- A straightforward and welcoming UK migration system to attract researchers, innovators, and their families.
- Continued UK participation in European Reference Networks for rare and complex diseases, to benefit patients in the whole of Europe.
- Maximum cooperation and harmonisation of frameworks governing regulation of medical research, medicines and medical devices. In particular, a pragmatic solution should be found so the UK can continue to engage with key regulatory bodies and shared infrastructures, including the new EU Clinical Trials Regulation.

How have patients benefited from the UK's collaboration in European research?

A Royal Society report demonstrates that 80 per cent of UK international research publications include co-authors from the EU.² Clinical research, including clinical trials, has benefited from UK and EU researchers working together, especially for rare and paediatric diseases where the UK has led or participated in the largest number of pan-European clinical trials.

As the number of patients with rarer conditions in each country is low, it is only possible to recruit enough patients for clinical trials by carrying out trials across countries. **A situation where UK trials are no longer able to recruit European patients would lessen the benefits for patients across the whole of Europe, as well as risk damaging UK and European science.**

Research is increasingly international and intrinsically collaborative. Scientific breakthroughs are not developed in isolation, as mobility is crucial to the highest standards of performance. Easy movement of researchers, innovators and specialist technicians encourages science to thrive in the UK and the EU by opening up access to skills and international networks.

International movement is a feature of researchers' careers, with 72 per cent of UK-based researchers spending time at non-UK institutions between 1996 and 2012. Moreover, 28 per cent of academic staff at UK universities are from outside the UK with 31,600 from other EU nations and 23,000 non-EU internationals.

EU funding programmes for research and innovation have supported and boosted these crucial cross-border collaborations. European funding is strategically different from national-level funding in the UK in that it incentivises collaboration and backs riskier and more discovery-led research. The funding itself is highly prestigious and has supported the careers of UK scientists, while creating networks of international scientific collaboration.

A recent report³ highlights the strong contribution the UK has played in EU medical research, including in clinical trials, leadership of scientific committees and panels, scientific training, and translational research. In the report, European survey participants

highlighted the UK's strong ability to conduct translational research to discover treatments and devices that can benefit patients across Europe. This has included developing a new generation of genetically targeted personalised medicines. **UK participation and coordination with the EU not only benefits the progression of medical research in the UK, but it also adds considerable value to medical research across the EU. Together, the UK and EU's medical research capacity is greater than the sum of its parts.**

The recent report from the high-level group chaired by Pascal Lamy on maximising the impact of European research and innovation programmes highlights the importance of collaboration for both Europe and the UK.

It states that "whatever Brexit modalities are agreed between the UK and the EU by 2019, full and continued engagement with the UK within the post-2020 EU R&I programme remains an obvious win-win for the UK and the EU. The UK has one of the strongest science bases of all European countries. A positive cooperation model, for example based on mutual investment, should be established, so that the UK remains part of the European Research Area."⁴

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Why is full and continued engagement between the UK and the EU a win-win for medical research post Brexit?

We believe the mutual benefits of collaboration in medical science and research can be used to build a bridge between the UK and the EU during very difficult negotiations. There are already some welcome signals from both the UK and EU that a successful solution is possible. The UK Future Partnership Paper on collaboration in science and innovation,⁵ which despite lacking detail, gave a strong positive signal of the UK government's intentions.

We also welcome the EU-UK joint report⁶ at the end of phase one of negotiations and the clarification it afforded on the participation of the UK in EU programmes, such as Horizon 2020. This report stated the UK "may wish to participate in some Union budgetary programmes of the new multiannual financial framework (MFF) post-2020 as a non-Member State."

Access to EU research and development funding could be retained, for example, through the UK gaining associate member status for Horizon 2020's successor (as achieved by Switzerland and Israel for Horizon 2020). This would also allow UK-based academics to lead and participate in EU-wide collaborations.

The UK is at the centre of Europe's work to understand the human genome

The Wellcome Sanger Institute was opened in 1993, in Hinxton near of Cambridge, as the leading partner in the global effort to sequence the first human genome. In 1994, the Institute was joined by the European Molecular Biology Laboratory-European Bioinformatics Institute (EMBL-EBI). EMBL chose to site their bioinformatics institute in Hinxton because of the presence of the Sanger Institute. Together, the two organisations have become the heart of an expanding and thriving hub of academic and commercial entities all working on genomics and biodata.

The two institutes now share the Hinxton campus with spin-outs, start-ups and Genomics England, the national genomics initiative tasked with sequencing 100,000 genomes of patients and introducing genomics into the UK National Health Service. The campus also hosts ELIXIR, an inter-governmental organisation that coordinates bioinformatics

infrastructure for Europe and Connecting Science, which runs conferences, advanced courses and public engagement events centred on genomics and human health. ELIXIR both collaborates in, and coordinates, a number of EU-funded research projects.

The result is a diverse group of organisations, and a multitude of formal and informal collaborations; a mixing of ideas and exchange of knowledge happen due to their close proximity. The Broad Institute, Boston, USA, and the Beijing Genomics Institute in China, are considered the closest comparators to the Hinxton hub, but neither have the breadth and depth of activity. The Hinxton campus is considered to have globally unrivalled capacity for genomics and biodata.

The Sanger Institute is core-funded by Wellcome, the UK-based foundation, and EMBL-EBI is primarily funded by participating countries. Together, the close partnership of the two institutes has created a local, European and global network of science that tackles the most challenging problems in science and health beyond the ability of any one organisation or country to address.

In the same vein, by the end of 2019, a consortium of life sciences companies is investing to sequence the exomes (the part of a genome that is translated, or expressed as proteins) of all 500,000 people within the UK Biobank resource, all with associated health records, creating an unprecedented resource linking human genetic variations to human biology and disease. This initiative is an unrivalled, pre-competitive big data resource for the world.

It is clear that Europe benefits from this exciting and crucial hub of research activity, and it would be regrettable if this collaboration were to be set back in any way as a result of Brexit. **UK health research could be limited by the UK's ability to access the talent from Europe that it needs to thrive.** Furthermore, many of the collaborations could be made significantly more complex. For example, divergence of standards on issues such as data protection could impact the endeavour to access crucial data from outside the UK. Although collaboration will continue after Brexit, any limitations on the ability of researchers and institutions to work together could diminish the impact of science across the whole of Europe.

Blueprint: EU-funded collaborative research success in blood disease therapy

[Blueprint](#) was launched in 2011 as the first high-impact research initiative funded by the European Commission. The five-year initiative brought together 41 leading European universities, research institutes and industry entrepreneurs from 12 countries, including nine EU member states.

Its mission was to understand how genes are switched on and off in blood cells from healthy individuals and patients with leukaemia. Blueprint studies explored normal and abnormal blood cell development and identified novel biomarkers to allow clinicians to distinguish between healthy and diseased blood cells.

Blueprint finished in 2016 after making a huge contribution to our understanding of cancer development and it delivered beyond initial expectations. The success of Blueprint was fuelled by critical inter-institutional collaborations, which were fostered through networking opportunities such as research symposia, laboratory exchanges, annual meetings and workshops that enabled the exchange of ideas and expertise.

Data from over 1,000 experiments and tools developed for interpretation have been made freely and openly available to the research community and continue to aid ongoing research. Blueprint resulted in more than 250 research papers on topics including nature, cell and science. A substantial programme of public engagement, education and training was also delivered through interactive training courses, workshops and podcasts.

Blueprint has provided profound new insights into the changes that occur in blood cells that turn cancerous. This knowledge has improved our understanding of leukaemia progression and prognosis, offers new targets for therapeutics and brings us closer to recognising the use of personalised medicine for cancer.

What is at risk if the right deal for science and research is not found during Article 50 negotiations?

Access to EU research and innovation funding schemes

Leaving the European Union means that the UK could become a 'third country' and lose its direct contact with EU research funding schemes. In fact, recent analysis shows that the UK's share of Horizon 2020 funding decreased by 20.5 per cent between 2015 and 2017. This may be, in part, attributed to the uncertainty that the UK leaving the EU presents to a number of potential European partners.⁷

The absence of a deal on the UK's future involvement in research programmes, although it would sometimes still be possible to collaborate in projects, means that UK organisations cannot benefit from EU funding, which would need to be sought from other sources.

It also means that outside of the EU, the UK will no longer be able to lead in developing the budgets, policies and programmes that make up the European Research Area.

Essential collaborations on rare diseases

The same is true for European Reference Networks (ERNs)⁸ on rare and complex diseases. These networks bring together healthcare providers across the EU/EEA to tackle rare medical conditions that require highly specialised treatment and a concentration of knowledge and resources.

Being an EU member state currently ensures that UK hospitals, clinicians and patients can benefit from these shared networks, and reciprocally, that EU networks benefit from the UK's competitiveness, particularly in the area of rare developmental disorders. These networks have been developed as a flagship programme for cross-border healthcare delivery for EU patients, as part of reciprocal healthcare rights agreed between EU member states.

Unless alternative arrangements are agreed during Brexit negotiations, the departure of the UK from the EU means that the UK can no longer continue as a member of ERNs or benefit from the associated shared IT infrastructure and EU funding. Meanwhile, the EU may see delays in benefiting from UK developments in diagnosing developmental disorders.

Migration of researchers

Free movement of people within the European Union has developed and enhanced a thriving pool of excellent scientists across Europe. The UK is a global science and innovation hub. Non-UK EU nationals make up around 17 per cent of science, technology, engineering and mathematics (STEM) academics at UK research institutions.⁹

Depending on the future migration system in the UK post-Brexit, European researchers and their families could be limited in their ability to move between the UK and EU27. This could limit their career choices and plans, which may result in them leaving the European region and finding positions in other regions. Research by UK universities suggests that 38 per cent of postgraduate students come from outside the UK.¹⁰ **Ensuring that European students are able to access globally competitive universities in the UK and retain them in the job market post-education is vital for UK and European science.**

Alignment and cooperation on medical research, medicines and medical technologies

The final, more complex, area is European legislation and the shared regulation of medical research, medicines and medical devices under the EU single market. The UK's departure from the EU means that, unless an alternative solution is found during the negotiations, the UK will be considered a 'third country' outside the EU's regulatory systems. Even if the UK chooses to mirror EU legislation nationally, it does not automatically mean the UK and EU can cooperate as they do now. **The UK needs to secure a future deal on how it will continue to take part in crucial regulatory bodies such as the European Medicines Agency, and shared infrastructures such as clinical trial databases.**

This poses particular problems for the authorisation and management of clinical trials, which is an EU regulated process. New EU legislation on clinical trials is due to be implemented in 2019. **Without agreement during Brexit negotiations, the UK will risk losing access to the crucial EU infrastructure that implements the legislation, such as the clinical trials portal and database which approve and regulate clinical trials. There are serious implications for patients access to medical research if the UK does not participate in the new EU Clinical Trials Regulation post Brexit.**

In the same vein, medical research and clinical trials can frequently require the transfer of personal data, which means that pan-European research benefits from shared regulation on protection of personal data. The new EU General Data Protection Regulation will be applied across the UK and EU from May 2018. **However, without an agreement from the European Commission that the UK's implementation of this data protection law is adequate, there could be significant problems in transferring personal data, in particular from the EU to the UK.**

Examples of the value of UK-EU cooperation on rare diseases

EU funding programmes and schemes facilitate research into rare diseases to a greater extent than national equivalents. Coordination of the much larger pan-EU population allows engagement of a sufficient cohort of both researchers with appropriate expertise and patients able to participate in research.

In 2014, EU grants worth over £190 million funded the investigation of rare diseases; this was more than the funding for either cancer or brain disorders. The UK is active in maintaining Europe's key registries and research networks in rare diseases. The UK

coordinates the highest number of European registries of all EU member states, including those for childhood lung diseases, Huntington's disease and familial pancreatic cancer.

The move towards personalised genetic medicine (an NHS priority), means that there will be an increased trend of research conducted into understanding subtypes of diseases which have fewer numbers of patients. This means there will, in effect, be more rare diseases. Being able to do research into these will require access to bigger populations, through collaboration. This means the need to collaborate is not restricted to the rare diseases of today, but must be there for the disease subtypes to be defined in the future.

Furthermore, in March 2017, 24 ERNs for rare diseases were launched by the European Commission. The NHS is involved in 23 of the 24 networks (approximately 40 NHS hospitals), with NHS trusts leading a quarter (six) of these networks. The legal basis for these networks is the European Directive on patients' rights in cross-border healthcare and thus membership is currently reliant on membership of the EU or EEA.

The value of clinical collaboration through ERNs in advancing research on rare diseases

As a consultant clinical geneticist and honorary professor in medical genetics in Manchester, Prof Jill Clayton coordinates a ERN on congenital malformations and rare intellectual disability. She works closely with colleagues across the EU on the diagnosis, management and treatment of rare diseases. Her patients benefit from her access to a wide pool of experts, specialist tests and clinical research. Jill is anxious that leaving the EU could jeopardise these links, which are not only useful for clinicians and researchers, but vital for patients.

Prof Chris Chapple, a consultant urological surgeon from Sheffield and coordinator of the ERN on rare urogenital diseases, says: "Knowledge sharing across our European Reference Network will foster innovation and allow better diagnosis, and new treatments and surgical techniques to be tested and made available to patients more quickly where there are gaps in current effective treatments... It is imperative that this incredibly exciting opportunity for greater collaboration through European Reference Networks is not jeopardised by the UK's political decision to leave the EU."

Prof Helen Cross from London is coordinator of the ERN on epilepsy and is concerned that Brexit could impact their work, which includes patients access to new treatments. She gives the example of Dravet syndrome, a rare early onset epilepsy with poor prognosis for seizure control and neurodevelopmental outcome. A European registry has been initiated and new cohort-relevant outcomes measures developed. Trials of new treatments have been completed, but the registry will enable knowledge of the positioning of these patients around Europe, and give them access to natural history and outcome studies.

Prof Kate Bushby Coordinates the ERN on rare Neuromuscular Diseases, from Newcastle. Kate explains: "Our ERN has the potential to reach out to several hundred thousand patients with neuromuscular diseases across Europe. These are exciting times for our community; for instance, 2014 saw the first European Conditional Approval of a therapy for a muscular dystrophy. Our field is fortunate in that we have robust infrastructures in place to improve trial-readiness for some of these conditions, thanks to initiatives like TREAT-NMD which arose from pan-European collaboration. Our ERN offers an unprecedented opportunity to optimise and expand on these achievements."

Recruiting patients to clinical trials on rare gynaecological cancers

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.

ENGOT's coordination activities are particularly relevant for research on rare gynaecological cancers. In Europe there are currently 4.3m people living with a rare cancer diagnosis. That's 22 per cent of the total cancer prevalence, yet outcomes in rare cancer treatment are consistently worse than those for patients with more common cancers.

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.

Throughout the process, researchers must travel 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.

According to Laura Farrelly, trials group lead at University College London 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."

So far, the UK has led or participated in the largest number of pan-EU clinical trials for rare diseases and paediatric treatments. Its participation in ENGOT and similar networks facilitates this success, and provides valuable connections and experience and that should not be lost.

Examples of the value of UK-EU cooperation on the development of medicines for children

The 2006 EU Paediatric Regulation¹¹ aims to promote high-quality research into the development of medicines for children. Specifically, it ensures that over time, the majority of medicines used by children are tested and authorised for such use. It has the

dual aim of obliging and incentivising industry to conduct paediatric clinical trials. It has certainly contributed to increased research in the EU, with the number of children in registered clinical trials jumping from 3,648 to 211,302 in the period 2006-2015. This 60-fold increase represents a significant growth in research involving children funded by the pharmaceutical industry.¹²

The BEACON clinical trial helps find the best treatments for children with rare cancer

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.

Neuroblastoma is a form of cancer that affects around 100 children, mostly under the age of five, every year in the UK. More than half the children with aggressive forms of the cancer will see it return, called recurrent neuroblastoma. And for these children, there are few treatment options left.

The BEACON-neuroblastoma trial aims to find the kindest and most effective combinations of drugs with which to tackle neuroblastoma. To do this, it is bringing together clinicians and scientists from ten European countries and two international consortia, with funding from Cancer Research UK and European partners.

This is the first randomised clinical trial to treat children with first relapsed neuroblastoma conducted across Europe and it hopes to recruit 160 patients in total. The trial itself was designed in the UK by Prof Keith Wheatley, scientific director at Cancer Research UK's Clinical Trials Unit in Birmingham.

"The BEACON-neuroblastoma trial has become a fantastic example of successful European collaboration," says Dr Moreno, chief investigator of the trial. "Such small patient populations make research into rarer cancers difficult, but all ten countries involved have joined forces to improve

things for children with poor prognosis cancers. We have involved patients and parents since the trial's inception, and numerous parent-led organisations support the trial as the best example of European collaboration to improve outcomes."

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 is 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.

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Brexit Health Alliance members

Co-chairs: Niall Dickson CBE • Sir Hugh Taylor

Secretary: Kate Ling

Members: Academy of Medical Royal Colleges • Association of Medical Research Charities • Association of British Healthcare Industries • Association of the British Pharmaceutical Industry • Association of UK University Hospitals • BioIndustry Association • Faculty of Public Health • Medical Schools Council • National Voices • NHS Confederation (including Mental Health Network, NHS Clinical Commissioners, NHS Employers, NHS Partners Network) • NHS Providers • Northern Ireland Confederation for Health and Social Care • Richmond Group of Charities • Scottish NHS Chief Executive Group • Welsh NHS Confederation.

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