Brexit and Beyond: Clinical trials

Summary

Aligned legislation and shared values underpin the UK and EU's extensive collaboration on clinical trials. This will change after Brexit, and the UK and EU have choices about whether, and how, to continue cooperating.

Options for the regulation of clinical trials in the UK after Brexit

We have analysed four realistic and achievable options for cooperation, assessing them in terms of their impact on collaboration, how burdensome they are, and their sharing of expertise.

The **best option for UK and EU clinical trials after Brexit is full UK participation in the EU clinical trials system on a similar basis to Member States**. The UK would implement the EU Clinical Trial Regulation (CTR) and have access to the single EU clinical trials portal and database alongside being a part of relevant regulatory discussions. This would enable the UK to continue its strong relationship with the EU on clinical trials, with access to EU resources, and provide a leadership role for the Medicines and Healthcare products Regulatory Agency (MHRA). The UK and EU should seek to agree this in future relationship negotiations, as it would minimise the burden on researchers, continue to provide access to the widest pool of patients, and allow Europe to use its collective expertise to be a global leader in clinical research. **In the interests of European health and research, both sides will need to be pragmatic in negotiations. A positive first step would be to include clinical trials in negotiations on the future UK–EU research and innovation relationship rather than the economic partnership.**

Exploring alternative options

Since achieving full UK participation will be challenging, this paper also examines possible alternatives and the costs and opportunities associated with these. All the alternative options involve significant trade-offs that would have an impact on UK–EU clinical trials.

- **Silent participation – the UK is a part of the system and has access to EU resources but cannot lead EU projects, vote on issues or raise objections**

This is like EEA countries' participation, such as Norway's (Table 1), and is essentially continuing the implementation period arrangements. Silent participation would be near identical to full participation for those conducting trials. However, the MHRA's role would be reduced, potentially diminishing the UK's leadership in clinical trials in the long term.

- **Independent and aligned – the UK is outside the EU system but mirrors the EU with its domestic arrangements**
  The UK would not have access to EU systems. Two systems would mean duplicate applications and reporting for UK–EU trials, but the burden can be minimised by keeping requirements aligned and having both sides recognise each other's processes.
- **Independent and divergent – the UK is outside the EU system and chooses to diverge completely and create a new clinical trials system**
  There is not time to implement a new system by the end of 2020. However, the UK could create a new system over time, for example building a new progressive alliance on clinical trial regulation. The risks and opportunities of such a bold approach would need to be carefully balanced.

Therefore, **if the full participation of the UK can't be negotiated, the UK should meet its commitment to put the CTR into law and should remain highly aligned to the EU framework in the short term, to minimise disruption.** Choosing a long-term alternative will not be straightforward, therefore **the MHRA should engage closely with academic and industry stakeholders on the options and trade-offs to agree the best alternative for the wide range of clinical trials taking place in the UK.**

Options for the regulation of clinical trials in the UK after Brexit

Background

Clinical trials are essential for bringing new medicines to people. They test whether new treatments are safe and effective and allow patients to access new medicines earlier.

Those running clinical trials must comply with a complex system of regulations, ethical guidelines and international standards (Figure 1). When this works well, it creates a supportive environment for research by protecting people, building public trust and driving innovation. When it goes badly, it creates confusion, costs and delays.

The UK regulatory environment for clinical trials generally works well. Led by the Health Research Authority (HRA) and Medicines and Healthcare products Regulatory Agency (MHRA), the system is science-led and risk-proportionate. Action has been taken to reduce the time needed to set up trials, for example with HRA providing single approval. In addition, there has been significant investment in clinical trial capability by the National Institute for Health Research (NIHR), helping over 660,000 patients take part in research in the NHS in 2016/17. It is estimated that clinical research supported by the NIHR Clinical Research Network has generated £2.4 billion and nearly 40,000 jobs[1].

This environment has helped make the UK globally competitive for clinical trials. Research funded by the UK government appears in leading clinical journals more than research from any other country. This lead grows if papers funded by UK charities such as Wellcome are also included[2].

The 'Impact of Collaboration' report demonstrates the depth of UK–EU collaboration on clinical trials. Over 4,800 UK–EU trials took place between 2004 and 2016[3]. Around 40 per cent of the trials currently running in the UK are being run with other Member States. Of these, around 1,500 trials have the UK as a sponsor, and half of these trials will still be ongoing in March 2019[4].

The UK makes a disproportionate contribution to Europe's clinical trial expertise and capacity, boosting European competitiveness. Besides holding 13 per cent of the EU's potential patient population, the UK runs the most early-stage phase I trials in Europe, and

[1] KPMG. NIHR Clinical Research Network: Impact and value assessment. KPMG; 2016. nihr.ac.uk/life-sciences-industry/documents/NIHR CRN Impact and Value FINAL REPORT_vSTC_160908_FOR EXTERNAL USE.pdf [accessed 4 February 2019]

[2] Journals: *Lancet*, *New England Journal of Medicine*, *Journal of the American Medical Association*, *BMJ*, *PLoS Medicine* and *BMC Medicine*. The Medical Research Council (61) and NIHR (87) bring a total of 148 publications. Adding charity funders (Wellcome, Cancer Research UK and the British Heart Foundation) this rises to 225. The US National Institutes of Health published 130 in total. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/650447/LifeSciencesIndustrialStrategy_acc2.pdf [accessed 4 February 2019]

[3] Varnai P et al. The Impact of Collaboration: The value of UK medical research to EU science and health – executive summary. CRUK; 2017. wellcome.ac.uk/sites/default/files/impact-collaboration-value-uk-medical-research-to-eu-science-health.pdf [accessed 4 February 2019]

[4] European Federation of Pharmaceutical Industries and Associations (EFPIA). BREXIT EFPIA Survey Results. EFPIA; 2017. efpia.eu/media/288531/brexit-survey-outcome-08112017.pdf [accessed 4 February 2019]

the second most phase II and III trials[5], which in total make up 25–30 per cent of all trials in the EU. The UK leads and participates in more pan-EU clinical trials on rare diseases than any other Member State[6], and ranks in the top four across the EU for clinical trials in mental health, cancer, cardiovascular disease and musculoskeletal disorders[7].

However, as the Life Sciences Industrial Strategy recognises, there is still potential to improve the UK clinical trials environment. NHS England's '12 Actions to Support and Apply Research'[8] paper will be important for making progress on trial set-up, and the second Life Sciences Sector Deal included further commitments to improve clinical trials[9].

Clinical trials legislation

Clinical trials are currently governed by the EU Clinical Trials Directive (CTD), with each Member State running separate regulatory approvals. This legislation covers only specific types of clinical trial, with other studies with human participants regulated under national law.

New legislation – the EU Clinical Trial Regulation (CTR) – will replace the CTD. The CTR was originally due to apply from 2016, but has been delayed until at least 2020 due to infrastructure problems[10]. Under the CTR, all trial applications, data and coordinated decisions from Member States will be communicated through a single portal. Although ethical approvals will remain a national competency, these will also come through the portal. Streamlined systems and communications will help simplify compliance with the CTR, potentially saving researchers in the EU £600 million a year, as well as offering savings of £60m a year to UK researchers[11].

[5] Association of the British Pharmaceutical Industry (ABPI). Open for Innovation: UK biopharma R&D sourcebook 2016. ABPI; 2016. abpi.org.uk/media/1358/open_for_innovation_abpi_sourcebook_2016.pdf [accessed 4 February 2019]
[6] Varnai P et al. The Impact of Collaboration: The value of UK medical research to EU science and health. CRUK; 2017. cancerresearchuk.org/sites/default/files/main_report_v8.pdf [accessed 5 February 2019]
[7] Varnai P et al. The Impact of Collaboration: The value of UK medical research to EU science and health – executive summary. CRUK; 2017. wellcome.ac.uk/sites/default/files/impact-collaboration-value-uk-medical-research-to-eu-science-health.pdf [accessed 4 February 2019]
[8] NHS England. 12 Actions to Support and Apply Research in the NHS. NHS England; 2018. england.nhs.uk/publication/12-actions-to-support-and-apply-research-in-the-nhs [accessed 4 February 2019]
[9] Gov.uk. £1.3 billion industry/government investment in UK economy and new partnership driving early disease detection. 5 December 2018. gov.uk/government/news/13-billion-industrygovernment-investment-in-uk-economy-and-new-partnership-driving-early-disease-detection [accessed 4 February 2019]
[10] European Medicines Agency (EMA). Clinical Trial Regulation – Implementation. ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation#implementation-section [accessed 4 February 2019]
[11] MHRA personal communication.

Brexit

Recommendation:

The best option for UK and EU clinical trials after Brexit is full UK participation in the EU clinical trials system on a similar basis to Member States. The UK and EU should seek to agree this in future relationship negotiations.

If the CTR comes into force either before or during the implementation period (29 March 2019–31 December 2020), it will be given effect in UK law through the EU (Withdrawal) Bill. In a speech to the House of Lords on 18 April 2018, Baroness Goldie confirmed the UK government's commitment to the CTR, even if it is delayed past 31 December 2020:

"If the CTR comes into force during the implementation period, as it is currently expected to do in March 2020, it will apply to the UK. If this opportunity does not come to pass, the Government will seek to bring into UK law all relevant parts of the EU regulation that are within the UK's control."[12]

If there is a withdrawal agreement, UK researchers would be able to lead EU-wide trials, and sponsors can be based in the UK, throughout the implementation period. However, the MHRA would not be able to lead on reviewing applications, a role known as being a 'reporting Member State'.

In the event the UK leaves the EU without a withdrawal agreement, there may be significant uncertainty over the legal arrangements for clinical trials. This is likely to disrupt current and future trials, potentially discouraging new investment by international pharmaceutical companies. Uncertainty already appears to be having an impact: we have heard of hesitancy to include UK researchers in collaborations, and it has been reported that the number of new clinical trials started in the UK has fallen[13], although this has been disputed.

[12] Hansard. European Union (Withdrawal) Bill. 18 April 2018, Volume 790. hansard.parliament.uk/Lords/2018-04-18/debates/D572CBF6-A85C-4208-B426-843747A766FA/EuropeanUnion(Withdrawal)Bill [accessed 4 February 2019]

[13] Reuters. UK clinical trials fall as Brexit clouds drug approval process. 18 October 2018. reuters.com/article/uk-britain-eu-pharmaceuticals/uk-clinical-trials-fall-as-brexit-clouds-drug-approval-process-idUSKCN1MJ1PG [accessed 4 February 2019]

2021 and beyond

After the implementation period, the UK and EU have choices about continuing their cooperation on clinical trials. We have explored the risks and benefits of four realistic options for academic trials (see Box 1), building on a paper by Cancer Research UK (CRUK)[14].

- **Full participation on a similar basis to Member States** – the UK continues its relationship with the EU for clinical trials almost unchanged, with access to EU resources like the single clinical trials portal and database and a leadership role for the MHRA.
- **Silent participation** – the UK is a part of the system and has access to EU resources but cannot lead EU projects, vote on issues or raise objections. This is like EEA countries' participation, such as Norway's (Table 1), and essentially continues the implementation period arrangements.
- **Independent and aligned** – the UK is outside the EU system but mirrors the EU with its domestic arrangements. The UK does not have access to EU resources, and UK regulators have no role in EU processes.
- **Independent and divergent** – the UK is outside the EU system and chooses to alter its processes for regulating clinical trials so that they no longer align with the EU.

Box 1. Options for future regulatory cooperation in UK–EU clinical trials

Around a quarter of UK clinical trial applications come from non-commercial organisations, such as universities or NHS Trusts[15]. Through discussions with the research community in the UK and EU, we have identified three factors that are essential if regulation is to support academic trials. Clinical trials regulation must:

- support collaboration and patient access
- be straightforward, simple and low-burden
- allow the easy exchange of expertise.

This section explores each of these three factors in turn against the above scenarios.

Support collaboration and patient access

In clinical trials, collaborating allows access to pools of participants large enough to deliver meaningful results. In our 'Brexit and Beyond' consultation, a group of European paediatric oncologists told us how this is especially important for them as they work on rare diseases with low patient numbers spread across Europe[16]. Easy access to wider patient pools has helped the UK to lead and participate in more pan-EU trials on rare diseases than any other Member State and host a quarter of the 24 European Reference Networks for rare diseases[17].

[14] CRUK. Future of Clinical Trials after Brexit – Final Report. CRUK; 2018. cancerresearchuk.org/sites/default/files/future_of_clinical_trials_after_brexit.pdf [accessed 4 February 2019]

[15] Between 2011 and 2015 an average of 30 per cent of UK trial applications came from non-commercial organisations. In 2016/17 this fell to 22 per cent, driven by falling non-commercial applications and rising commercial ones.

[16] Wellcome. Future Partnership Project: Consultation on the future EU–UK relationship on research and innovation. Wellcome; 2018. wellcome.ac.uk/sites/default/files/consultation-on-future-eu-uk-relationship-on-research-and-innovation.pdf [accessed 5 February 2019]

[17] Varnai P et al. The Impact of Collaboration: The value of UK medical research to EU science and health. CRUK; 2017. cancerresearchuk.org/sites/default/files/main_report_v8.pdf [accessed 4 February 2019]

Together the UK and EU have the critical mass of expertise and patients needed to conduct robust trials – with a total population larger than the USA. The importance of this is shown by the current extent of UK and EU collaboration: 40 per cent of UK-based trials also have a site in the EU. This collaboration has helped Europe to become a major hub for clinical trials – when working together the EU runs almost as many trials as the USA[18].

Full or silent participation option would enable this to continue. However, the potential for UK–EU collaboration would be compromised in either independent option, as this would reduce easy access to such a large patient pool. Those setting up trials may choose to locate them in the EU or UK – or locate them outside Europe altogether, in favour of other countries with access to large pools of patients and that are rapidly expanding their clinical trial offer, such as China. Reducing the effective patient pool in Europe could therefore damage both EU and UK competitiveness.

Be straightforward, simple and low-burden

Setting up a trial is complex and burdensome (Figure 1). The Medical Research Council's Clinical Trials Unit reports that it takes three to six months for a half-time employee to complete an EU clinical trial authorisation dossier[19]. We've heard of one Framework Programme 7-funded trial that was due to take place in 20 sites around Europe, only for it never to happen due to the length of time the grant took to set up.

Full or silent participation would be the best way to minimise the burden on researchers running trials across the UK and EU. UK researchers would benefit from the single application portal, making it easier to set up and run trials in the UK and EU. Both the UK and EU would recognise sponsors in the other's jurisdiction and there would be no additional burden, making it easy to lead pan-European studies from the UK or EU.

In either independent option the burden of running trials would be increased. UK-led trials would be regulated under a different law to their EU sites. A legal representative would likely be required in both jurisdictions, increasing cost, as well as taking on legal risk. This would disproportionately affect academic trialists as the universities and NHS Trusts they work for are unlikely to have existing in-country representatives compared to industry[20].

Researchers would need authorisation in both the UK and EU to run a trial, duplicating application dossiers and reporting. This could be minimised by making UK application requirements identical to the EU as in the independent and aligned option. However, additional reporting – for example on safety data – would likely still be necessary. For those setting up trials in the EU who already have sufficient access to pools of participants this may be off-putting, however low the burden is.

Both independent options give the UK the opportunity to make domestic reforms and minimise the burden on researchers, but to different degrees. Significant divergence is likely to compromise EU recognition of the robustness of UK processes, which is critical for success in the independent and aligned option, reducing the flexibility available. Reform is also limited by the need to ensure continuing high levels of patient safety. The benefits of diverging from EU standards to reduce burden and facilitate trials would need to be weighed

[18] Association of the British Pharmaceutical Industry (ABPI). Open for Innovation: UK biopharma R&D sourcebook 2016. ABPI; 2016. abpi.org.uk/media/1358/open_for_innovation_abpi_sourcebook_2016.pdf [accessed 4 February 2019]

[19] Personal communication.

[20] In the event of no deal, the MHRA has suggested moving sponsorship to the chief investigator where the legal sponsor is outside the UK. It is unclear how this would work for UK-led EU trials.

against the fact that different standards will make multi-country trials more difficult. In our 'Brexit and Beyond' consultation, CRUK reported that this has made some EU–USA trials unfeasible[21].

Allow the easy exchange of expertise

By sharing approaches and knowledge between regulators and academia, trials can be better designed, run and regulated. The easiest way for the EU to continue to benefit from the UK's expertise, and vice versa, is through full participation. The MHRA is a valued and respected medicines regulator in the EU. Between 2008 and 2016, the MHRA was appointed as Scientific Advice Coordinator by the European Medicines Agency (EMA) on 20 per cent of centralised medicine approval procedures, and provided data to 50 per cent of all decentralised medicine approval procedures[22] – more than any other regulator[23]. In 2016 the MHRA was nominated as the reference Member State for over 30 per cent of Voluntary Harmonisation Procedures, leading the coordination of clinical trial approvals taking place across multiple EU sites.

Under all these options the UK could not vote on clinical trials-related legislation. However, under the full participation option the MHRA could lead clinical trial authorisations as a reporting competent authority. Under silent participation, the MHRA could not take a lead in reviewing applications, reducing the sharing of expertise that can help problem solving in trials regulation. Independence would give the UK the freedom to develop innovative regulation, but the ability of the UK to spread this to other countries would be limited outside a formal collaborative bloc.

How can full participation be achieved?

Recommendation:

To realise the mutual benefits of full UK participation, both sides will need to be pragmatic in negotiations. A positive first step would be to include clinical trials in negotiations on the future UK–EU research and innovation relationship rather than the economic partnership.

Taking together the factors vital to supporting clinical trials, full participation of the UK is the best option for UK and EU clinical trials after Brexit. Primarily, it allows both blocs to continue sharing trials under shared European values. It also minimises the burden on researchers, continues to provide access to the widest pool of patients, and allows Europe to use its collective expertise to globally lead in clinical research. However, full participation is a challenging ambition to meet. This section sets out how it could be achieved.

[21] Wellcome. Future Partnership Project: Consultation on the future EU–UK relationship on research and innovation. Wellcome; 2018. wellcome.ac.uk/sites/default/files/consultation-on-future-eu-uk-relationship-on-research-and-innovation.pdf [accessed 5 February 2019]
[22] Stafford Lightman. European Science and Brexit. Royal Society, British Neuroscience Association and the Academy of Medical Sciences. nhsconfed.org/-/media/Confederation/Files/public-access/EU-Parl-Event-27092018/Stafford-Lightman-British-Neuroscience-Association.pdf [accessed 5 February 2019]
[23] Politico. Hosting the EMA: who's dead serious, who's along for the ride? 21 August 2017. politico.eu/article/brexit-ema-european-medicines-agency-hosting-who-is-dead-serious-and-who-along-for-the-ride/ [accessed 5 February 2019]

Negotiations will start from a helpful point, as the future framework declaration indicates the UK and EU will align standards in areas like pharmaceuticals. Nevertheless, reaching agreement will **require both sides to be pragmatic.**

The **UK must meet its commitment to put the CTR into law** while recognising that this comes with a financial cost and requires respect for European Court of Justice jurisdiction[24]. Harmonised legislation isn't enough. For full participation to work in practice the **UK must also negotiate access to the EU's clinical trials portal and database**. The UK will lose its vote in EU institutions on clinical trials legislation but would retain involvement in regulatory processes.

Creativity would be needed from the EU's perspective. There is no precedent for those outside the internal market participating on a similar basis to Member States. Even Norway, inside the EEA, cannot lead regulatory dossiers (Table 1). There are also no examples of existing free trade agreements that provide this level of cooperation.

However, the depth of the UK's contribution to EU health research, and the additional opportunities for EU-based patients, mean it is in the EU's interest to find a route to full participation. A positive first step would be to include clinical trials in negotiations on the future UK–EU research and innovation relationship rather than the economic partnership. The EU has deep research relationships with several third countries, acknowledging the benefits they bring to European citizens. Continuing to collaborate on trials would be in keeping with this tradition.

Table 1. Interaction of other countries with EU clinical trials

Norway	**Switzerland**	**Canada**
European Economic Area	**European Free Trade Agreement**	**Third Country**
Organisations in Norway can sponsor clinical trials within the EEA without having a legal representative in the EU. When the CTR is in place, Norway will be part of the new single portal and databases. Unlike an EU Member State, the Norwegian competent authority does not have a leadership role.	Organisations in Switzerland can sponsor clinical trials within the EU but must have a legal representative in the EU to do so. Running a trial in the EU and Switzerland requires two applications: one to the competent authority in each area. Swiss clinical trials are regulated by independent national legislation, such as the Therapeutic Products Act (2000) and the Human Research Act (2011). Switzerland runs its own research portal and in EU legislation is considered a third country, ie a country outside the EEA that must have a legal representative in the EEA to run a clinical trial there.	Organisations in Canada can sponsor clinical trials within the EU but must have a legal representative in the EU to do so. Running a trial in the EU and Canada requires two applications: one to the competent authority in each area. Canada has its own independent national regulation, runs its own research portal and in EU legislation is considered a third country, ie a country outside the EEA that must have a legal representative in the EEA to run a clinical trial there.

[24] As recognised in the Brexit White Paper. Department for Exiting the European Union. The Future Relationship between the United Kingdom and the European Union. Department for Exiting the European Union; 2018. gov.uk/government/publications/the-future-relationship-between-the-united-kingdom-and-the-european-union [accessed 5 February 2019]

Exploring alternative options

Recommendation:

If full participation of the UK can't be negotiated:

- **The UK should meet its commitment to put the CTR into law and remain highly aligned to the EU framework in the short term, to minimise disruption.**
- **The MHRA should engage closely with academic and industry stakeholders on the options and trade-offs to agree the best alternative for the wide range of clinical trials taking place in the UK.**

Since it will be challenging to achieve full participation of the UK , we have also examined three possible alternatives, all of which involve significant trade-offs that would have an impact on UK–EU clinical trials. This section explores these, and looks at how the potential downsides could be mitigated. If the UK cannot secure full participation, choosing an alternative will not be straightforward. It will be important to weigh up the short- and long-term opportunities and costs for the wide range of trials taking place in the UK. To inform its approach, the MHRA will need to engage closely with academic and industry stakeholders.

Silent participation

For UK researchers and sponsors running clinical trials, silent participation would be similar to being a Member State. Researchers could lead trials and collaborate with their colleagues in the EU27 easily, allowing more opportunities for UK and EU patients to take part in research. This would minimise disruption to trials and could therefore be a good option in the short term.

However, access to EU infrastructure, such as the portal, would have to be negotiated, which may require a significant investment of time and negotiating capital. Diverging after negotiating silent participation may be challenging depending on what is included in the UK–EU agreement. This could reduce the flexibility open to the UK in the longer term.

In recent times the UK has been selected less frequently to lead Voluntary Harmonisation Procedures, which suggests that silent participation may undermine the MHRA's leadership role and harm the UK's clinical trial environment. In the longer term the lack of high-profile work could impact the MHRA's ability to attract talent, in turn reducing its ability to innovate. The MHRA played a key role in shaping the current trials landscape in the EU; with reduced MHRA influence, the EU approach could move in a different direction, for example becoming more risk-averse. The potential long-term degradation of the UK clinical trial environment as a result of silent participation may therefore not be worth the short-term benefits of minimising disruption.

Independent and aligned

Compared to silent participation, a highly aligned model would be less attractive in the short term as applications and reporting would be duplicated, as discussed above. However, keeping requirements identical would minimise the burden, and the UK could seek mutual recognition agreements with the EU on regulatory processes to minimise duplication. This would mean both sides would deem the other's trial applications, inspections and authorisations as equivalent in safety to their own. It may be easier to negotiate mutual

recognition than a closer relationship, particularly as the UK will start from the same legislation. Although there are clear downsides to duplication, this should be weighed against the flexibility this option gives the UK. For instance, the MHRA could build on its regulatory leadership by offering a highly responsive service and enhancing its processes, for example to make the approval of single-country studies globally competitive. Remaining highly aligned could therefore be a pragmatic short-term compromise between continuity and UK leadership in clinical research.

Independent and divergent

Under an independent model, the UK would have the freedom to diverge completely and create a new clinical trials system. In the short term this option is not practical, as there is not enough time to create a fully-fledged system or to negotiate alignment with another jurisdiction by the end of 2020. However, starting from a highly aligned model, the UK could create a new system over time. Careful consideration would need to be given to the whether the benefits of full divergence outweigh the short-term resource needed to create and implement a new system, and the risks of leaving an established and competitive system. The UK could choose to align with a different jurisdiction, such as the USA, through trade negotiations. However, it is very difficult to envisage any other country agreeing to a level of UK involvement that would make this worthwhile. Alternatively, it could be possible for the UK to establish a progressive alliance of like-minded regulators, like Switzerland or Canada, to create a competitive and innovative regulatory system covering a wide pool of patients and expertise. This may be an attractive long-term approach, but achieving this relies on the decisions of other sovereign countries, and it would be complex and time-consuming to build a new and close framework from scratch.

Annex – options analysis of future UK–EU cooperation on clinical trials

Full participation

- The UK continues its involvement in EU clinical trials almost unchanged.
- The UK implements the CTR, fully aligning its regulation with the EU.
- The EU grants the UK access to the single clinical trials portal and its associated database.
- Trials can therefore be sponsored from the UK without an EU legal representative, and UK-based researchers see no difference to their EU27 counterparts in applications or roles.
- The MHRA continues leading regulatory work and related EU projects. The UK is fully involved through observer status in relevant committees and meetings but loses voting status.

Opportunities	**Risks**
UK researchers continue to benefit from a harmonised system across the EU and a single application portal, reducing the burden on researchers setting up and running trials. Single notification in attractive timeframes. Decisions coordinated across Member States. Reporting also coordinated.	The UK cannot diverge from the regulation or regulatory processes.
UK researchers and institutions can continue to sponsor and lead multi-state trials without requiring a legal representative in the EU.	The UK loses opportunities for national discretion and is possibly obliged to implement related EU policies on medicines, devices or clinical research.
The MHRA as a national competent authority can still take part in multi-state CTR applications and be a reporting member state.	
The UK maintains soft influence through expert involvement and presence in key meetings.	
The EU system for managing compliance issues. The UK benefits as it's able to share the burden with Member States in the assessment and management of breaches.	
The UK has access to Member States' inspection reports, to share information and approaches and allow joint decisions.	

Silent participation

- The UK implements the CTR, participates in the EU's harmonised clinical trials system, and is granted full access to the clinical trials portal and database by the EU.
- UK researchers can lead trials, and sponsors can be based in the UK.
- The MHRA does not have a formal role and is excluded from reviewing regulatory dossiers or providing scientific advice.

Opportunities	**Risks**
UK researchers continue to benefit from a harmonised system across the EU and a single application portal, reducing the burden on researchers setting up and running trials. Single notification in attractive timeframes. Decisions coordinated across Member States.	The UK cannot diverge from the regulation or regulatory processes.
UK researchers and institutions can continue to sponsor and lead multi-state trials without requiring a legal representative in the EU.	The UK loses opportunities for national discretion and is obliged to implement other related EU policies.
The EU system for managing compliance issues. The UK benefits as it's able to share the burden with Member States in the assessment and management of breaches.	The MHRA no longer has a role in implementing and developing European legislation and guidance.
The UK has access to Member States' inspection reports, to share information and approaches and allow joint decisions.	The UK cannot take part in multi-state CTR applications and be a reporting member state.
Clarity and stability because there is no disruption to systems and a clear way forward.	

Independent and aligned

- The UK adopts the CTR and aligns its processes and systems with the EU. However, the UK no longer plays any part in EU sharing of dossiers and loses access to the single portal for clinical trials.
- This produces a parallel system, whereby the UK accepts EU applications, but they must be submitted twice, once to each authority.
- The EU may recognise the UK's regulatory processes for clinical trials but still require a legal presence in the EU and an EU application to set up a clinical trial. This could provide the UK with flexibility to explore relationships with regulators outside the EU.

Opportunities	**Risks**
The UK could respond to applicants faster than the EMA, bringing forward trial start times.	To run a clinical trial in the UK and EU, researchers submit two applications and receive feedback on both. This, and reporting requirements through two systems, will increase the time and cost burden. This might reduce the incentive to apply in the UK, potentially decreasing UK-based trials and therefore limiting opportunities for UK patients.
The UK is not bound by European decisions.	UK researchers could sponsor multi-state trials, but would need an EU legal representative (or at least a contact point). This is likely to be costly, especially for university sponsors, which lack existing legal structures to do this.
Sponsors could benefit from a UK-only system that is more responsive and tailored to their needs, for example being faster and more risk-proportionate. Sixty per cent of trials run in the UK are UK-only.	The UK needs to accept the same applications, documentation and materials as the EU. This would require the UK to recognise the legal responsibility of the EU27. This is critical in the short term to prevent significant upheaval.
Organisations may use the UK's swift/lower-burden processes to test clinical trials and applications before upscaling through the EMA.	No European influence. The MHRA no longer has any input in implementing and developing European legislation and guidance.
	Inspection planning and conduct could be hindered by lack of supporting information from the EU. The UK could look to the US example to mitigate this; for example, agreements are in place between the EU and USA on good manufacturing practice inspections for pharmaceuticals, with accompanying confidentiality arrangements, which minimises duplication and enables the US Food and Drug

	Administration to share full inspection reports of medicine manufacturers.
In the medium term, the UK could learn from developing approaches to ensure ongoing collaboration with the EU on clinical trials and use this knowledge and experience to establish progressive alliances with other regulators. This will allow the UK to grow its role as global regulatory leader.	Designing an entirely new system with smaller innovative regulators, like Canada or Switzerland, is not possible in time for the UK's exit. The CTR took many years to develop and has yet to be implemented. The time taken to design a system supported by researchers, the public and evidence will be significant.

Independent and divergent

- The UK establishes a new, divergent system to deliver clinical trials. Cross-European trials require two separate and different approval processes.
- The UK does not recognise the EU's regulatory processes and vice versa.
- The UK cannot lead cross-EU clinical trials and requires a legal representative or sponsor in the EU and UK to collaborate.
- The UK may explore relationships with other regulators or countries, like the USA, Canada or Switzerland, for clinical trials, adopting standards that more closely link with these jurisdictions.

Opportunities	**Risks**
The UK could respond to applicants quickly and increase risk proportionality. The UK could be a testing board for a swift approval before scaling up trials to other jurisdictions.	With divergent approaches, such as a testing lower-burden, faster approvals, other regulators may not recognise the outputs of UK-only trials. This could reduce the incentive to run a UK trial if the EMA does not accept data produced from it.
The UK is not bound by European decisions or alliances with any other countries.	The administrative burden of multi-country trials could see the UK excluded by sites like the EU, which have streamlined processes to access broader pools of patients. The number of clinical trials in the UK might decrease, as some organisations will not make a separate application to the UK. Fewer trials in the UK limits opportunities for UK patients.
Most trials run in the UK are UK-only. Sponsors may benefit from a UK-only system.	Designing a new system in time for the UK's exit is not possible. Although a single country could likely act faster, the time needed to design a system supported by researchers, the public and evidence will be significant. However, in the longer term a new system could be tailored towards UK-only trials, or developed in collaboration with other innovative second-tier regulators, like Canada or Switzerland.
	The relatively small population of the UK alone will not be sufficient to run large clinical trials or those for rare diseases; researchers will not be able to recruit from a large enough pool of patients and therefore the results may not be as robust.