Communication to sponsors of clinical trials and clinical investigations in the event that the UK leaves the EU without a deal

Target audience: Sponsors of commercial and non-commercial clinical trials and clinical investigations involving patients being conducted in the UK including industry, universities, NHS Trusts and charities; entities running clinical trials and clinical investigations on behalf of sponsors e.g. Clinical Research Organisations (CROs) and Clinical Trial Units (CTUs); trade associations e.g. AMRC, ABPI, BIA, BIVDA, ABPHI; research charities including CRUK and BHF; University Hospital Association, R&D Directors' Group and Medical Schools Council.

Introduction

The UK Government has now agreed an extension to Article 50. If the Withdrawal Agreement is approved by the House of Commons this week, the exit date will be confirmed for 11pm on 22 May (UK time). If the Withdrawal Agreement is not approved by the House of Commons, the legal default in UK and EU law is that the UK will leave the EU on 12 April 2019 without a deal. Therefore, as a responsible government must plan for every eventuality, including a no deal scenario on 12 April.

The Department of Health and Social Care (DHSC) has communicated widely with industry (via trade associations), the NHS and charities (via Association of Medical Research Charities), and Universities, and has emphasised that **organisations running clinical trials and clinical investigations in the UK should consider their supply chains for supplies (including Investigational Medicinal Products, devices/in-vitro diagnostics devices, advanced therapy medicinal products, radioisotopes and other clinical consumables)** to ensure appropriate arrangements are in place to assure supplies in the event of any possible border delays.

Sponsors are asked to:

- continue to mobilise their own plans for EU Exit operational readiness;
- have systems in place for monitoring stock positions and supply chain performance that allow for developing issues to be identified at the earliest opportunity;
- have in place effective procedures for monitoring and managing demand to detect and challenge excessive ordering, and control stock despatches and;
- have put in place the necessary governance structures and approvals processes to allow for rapid response and collaboration with the NSDR on supply disruption incidents;
- ensure that customer service functions are adequately resourced and equipped to manage an increase in enquiries, in the event that supply disruption events do start to impact care providers and patients;
- ensure processes are in place for the rapid reporting of all supply disruption incidents (including potential incidents) through the National Supply Disruption Response (NSDR is described in detail below) – the sooner the NSDR is informed of an incident or potential incident, the sooner it can take action to ensure providers and patients receive the products they need on time.

Should sponsors, or other organisations running clinical trials/investigations, become aware of any issues regarding supply, two key contacts have been established, and are discussed in further detail in this document.

- **Queries or early intelligence on potential issues/concerns related to EU exit – DHSC Clinical Trials Disruption Response Group: ctcontingencyplanning@dhsc.gov.uk**
- **General queries to the MHRA**
  - **Telephone (weekdays 8:30-16:30): 020 3080 6456**
  - **clintrialhelpline@mhra.gov.uk**
- **UK and Pan European trials**
  - **MHRA Clinical Trials Helpline: 020 3080 6456**.
- **Immediate notification of a supply disruption where support is needed to resolve - DHSC National Supply Disruption Response (NSDR):**
  - **Freephone number in the UK: 0800 915 9964**
  - **Direct line: 0044 (0) 191 283 6543**
  - **Email: supplydisruptionservice@nhsbsa.nhs.uk (available from 27 March)**

Trial sites should contact the clinical trial/investigation sponsor or the organisation running the clinical trials/clinical investigation using established processes to resolve the issue.

This document provides information and links to published guidance addressing the following areas:

1. **Clinical Trials and Clinical Investigations Supplies**
2. **Shipping Routes between the EU and the UK and Warehousing space**
3. **Trial sites storing additional stock of clinical trial supplies**
4. **National Supply Disruption Response (NSDR)**
5. **Data**
6. **Transport by air**
7. **Customs Procedures at ports, including airports**
8. **Importing and Exporting tissues and cells, including biosamples**
9. **Guidance on submitting MHRA clinical trials submissions**
10. **Import Licences for Investigational Medicinal Products**
11. **Further guidance and other areas of interest**

1. Clinical Trials and Clinical Investigations Supplies

Established processes and systems should already exist for responding to serious supply disruption events for clinical trial/investigation supplies and these systems should continue to be used; for example, trial sites should seek to resolve the issue through the sponsor of the clinical trial or investigation, or through the organisation running the clinical trial/investigation e.g. CRO or CTU.

DHSC understands the exit from the EU without a deal represents risks to the continuity of supply of products for clinical trials and clinical investigations. Therefore, as part of our contingency planning, we have conducted a comprehensive analysis of all live and in set-up clinical trials and clinical investigations funded and/or supported by the NIHR in England and trials/investigations within Northern Ireland,

Scotland and Wales. These trials are sponsored and funded by a range of industry, public and charity organisations. This analysis informed our understanding of which clinical trials and clinical investigations are dependent on supplies coming from or via the EU27/EEA, and gaining assurance from sponsors on the state of the preparedness and contingency planning for any possibly disruptions to clinical trials and clinical investigations supplies.

While the DHSC is working very closely across government and with NHS England to limit any impact of the UK leaving the EU without a deal on clinical trials/investigations, early intelligence of any potential or developing issues would help the DHSC consider any action at the earliest opportunity, ideally before the disruption has occurred.

Action required: The Clinical Trials Disruption Response Group in DHSC would welcome sponsors, or other entities running clinical trials and clinical investigations supplies, getting in contact as soon as they are aware of an issue with supply by emailing ctcontingencyplanning@dhsc.gov.uk.

2. Shipping Routes between the EU and the UK and Warehousing space

To address potential border delays should the UK leave without a deal, on 18 February Steve Oldfield, Chief Commercial Officer at the DHSC, wrote to all sponsors to provide more operational details of two specific elements of the Department's contingency measures to maintain continuity of supply of clinical trial supplies:

- ferry capacity (DHSC Dedicated Shipment Channel) has been secured to transport prioritised products, including clinical trial/investigation supplies. These will be available as an alternative supply route for companies moving these products into the UK. All sponsors of clinical trials/investigations should have received guidance on the prioritised shipping routes and a link to register.
- Warehousing space has been secured to facilitate storage of clinical trials/investigations supplies should it be needed

If a sponsor has not received this letter from Steve, the accompanying guidance or the subsequent link to register onto the portal 'DHSC eXchange', then please contact the Department as soon as possible by emailing ctcontingencyplanning@dhsc.gov.uk

3. Trial sites storing additional stock of clinical trial supplies

It is the responsibility of clinical trial/investigation sponsors to ensure continued supplies for their clinical trial/investigation. Clinical trial/investigation sponsors should not ask study sites to hold additional clinical supplies or stock where this is managed/supplied through the routine NHS supply chain. Any clinical trial/investigation supplies which are provided via the routine NHS supply chain should be managed as for all other medical supplies. Providers should not stockpile or hold additional stock.

For specific clinical trial/investigation supplies which are provided by trial sponsors, in exceptional circumstances, a case could be made for holding short-term additional stock locally, calculated by patient need, recruitment rates/numbers and the

anticipated extended time between placing an order and receiving the clinical trial product. This would need to be agreed locally and would depend on availability/capacity of adequate appropriate storage space and storage requirements e.g. temperature controlled. However, sites should not be expected to hold stock for whole trial periods (unless very short) or for other sites in the study. Where holding additional trial stock may impact on stock supplied via the routine NHS supply chain (i.e. open label studies) then the default should be referral to the central process.

4. National Supply Disruption Response (NSDR)

Each trial/investigation should have established processes and systems in place for responding to serious supply disruption events for clinical trial/investigation supplies and these systems should continue to be used; for example, trial sites should seek to resolve the issue through the sponsor of the clinical trial or investigation.

While DHSC has every confidence that the measures put in place by sponsors and the Department will provide continued access to clinical trial/investigation supplies, it important that the DHSC is prepared to respond to supply disruption incidents should they occur.

As part of its Operational Response Centre, the Department of Health and Social Care has set up a National Supply Disruption Response (NSDR). The NSDR processes will monitor the supply situation and co-ordinate actions to address supply disruption incidents that occur after the UK has exited the EU where normal procedures are unable to provide a resolution.

How will the NSDR work?

- The NSDR includes a call centre to record supplies disruption concerns from any source, and route them correctly;
- The NSDR unit will coordinate suppliers/sponsors, the health services and social care and central Government to resolve incidents, minimising impact on care provision and patients;
- It will offer logistics trouble-shooting to suppliers/sponsors whose consignments are stuck in border disruption which includes getting the supplies onto the Department of Health and Social Care Dedicated Shipment Channel; and
- Supply disruption issues that are not purely logistical will be immediately passed to teams that can resolve them, using scaled up existing business as usual processes.

The following actions should be taken where an organisation involved in delivering a clinical trial/investigation experiences a supply disruption to products or services

- A sponsor or an organisation running a clinical trials/clinical investigation experiencing disruption to normal supply chain regardless of the cause should use existing processes to resolve the issue.
- A trial site should contact the clinical trial/investigation sponsor or the organisation running the clinical trials/clinical investigation using established processes to resolve the issue.
- Sponsors/organisations running the clinical trial/investigation should notify NSDR immediately

    - of any issues relating to normal supply routes, or any potential risks that are likely to impact their ability to ship clinical trial/investigation supplies into the UK on schedule, including their proposed contingency resolution where possible. These issues may or may not be related to the UK's exit from the EU and may include problems such as component or raw material shortages, regulatory challenges or delays, logistics or transportation problems, etc.;
    - to allow as much time as possible to assess the urgency and nature of the issue, and help to identify actions to mitigate impact on patient care and integrity of the clinical trial/investigation;
    - of any direct communication to clinical trial/investigation sites that are planned or that have been issued in relation to emerging clinical trial/investigation supply disruption issues;
- In reporting issues to the NSDR, sponsors will be asked for detailed information to help the DHSC teams determine the most appropriate response, for example;
    - details of the disruption and causes,
    - anticipated duration of disruption,
    - products affected and product characteristics e.g. storage conditions, short shelf life,
    - criticality of products for patient care,
    - potential alternative products within your range or available from other suppliers,
    - the likely impact of the disruption,
    - how many healthcare providers and/or patients that could be affected (for the whole of the UK and/or by region/country as applicable).
- For other queries or to report potential issues/concerns relating to the EU exit please continue to use ctcontingencyplanning@dhsc.gov.uk

If a sponsor experiences disruption to any part of its normal supply routes, with no immediate resolution available, they should report it to the NSDR unit on

- **Freephone number in the UK: 0800 915 9964**
- **Direct line: 0044 (0) 191 283 6543**
- **Email: supplydisruptionservice@nhsbsa.nhs.uk (available from 27 March)**

5. Data

It is important that all organisations, as a priority, review whether they would be affected by the UK leaving the EU without a deal by assessing their data flows. For those that would be affected, early action is strongly advised as changes may take some time to implement.

Inbound personal data flows from the EEA may be affected. DHSC recommends that sponsors identify inbound personal data flows, which are data transfers from any EEA organisation to its organisation. DHSC would also recommend that sponsors contact these EEA organisations to discuss and put in place the relevant appropriate safeguards. Please note that these safeguards can be implemented now.

Relevant guidance has been published by

- NHS England - sets out action that need to be taken to ensure continued access to, processing and sharing of personal data https://www.england.nhs.uk/publication/eu-exit-personal-data/
- Information Commissioner's Office (ICO) - sets out data protection considerations in the event the UK leaves the EU without a deal https://ico.org.uk/for-organisations/data-protection-and-brexit/data-protection-if-there-s-no-brexit-deal/
- Health Research Authority (HRA) – provides links to relevant guidance relating to transferring research data between countries in the event of a 'No Deal' EU Exit via the website. The HRA's page will be updated with any new relevant guidance issued. https://www.hra.nhs.uk/about-us/news-updates/latest-guidance-implications-nodeal-brexit/

6. Transport by air

The Department for Transport's aviation technical notices and the EU's published plans for aviation contingency preparations, updated with proposed EU regulations on 19 December, clearly demonstrate that, in the event of no deal, both sides are committed to maintaining connectivity. The flexible movement of air cargo across Europe is in everyone's interests, and the EU has established mechanisms to recognise the cargo security standards of other countries. The EU has said (30 November) that it would recognise UK cargo security standards in the event of a 'no deal' exit which would allow for the continued flow of cargo.

7. Customs Procedures at ports, including airports

DHSC is aware that a significant proportion of clinical trials and clinical investigations supplies, including the transport of biosamples, are transported by air. The current Customs Freight Simplified Procedures (CFSP) used for exports will continue to be available should the UK leave the EU without a deal.

HM Revenue & Customs (HMRC) and has developed the *Partnership pack: preparing for changes at the UK boarder after a no deal EU Exit* which provides a high-level guide to the processes and procedures that are likely to apply to cross-border activity between the UK and the EU in a no deal scenario.

https://www.gov.uk/government/publications/partnership-pack-preparing-for-a-no-deal-eu-exit

HMRC has brought together a set of guides about trading with the EU in the event the UK leaves without a deal. It includes information on importing/exporting goods and customs procedures
https://www.gov.uk/government/collections/trading-with-the-eu-if-the-uk-leaves-without-a-deal

Customs procedures which apply to the importation of goods into the UK from places outside the Community, from the time of their arrival until they are entered to free circulation or another Customs procedure.

- https://www.gov.uk/government/publications/notice-199-imported-goods-customs-procedures-and-customs-debt/notice-199-imported-goods-customs-procedures-and-customs-debt

HMRC has undertaken a webinar '*Preparing for a no deal EU Exit: what businesses need to be aware of*'
https://www.youtube.com/playlist?list=PL8EcnheDt1zjoo7bz6y_HJBFtPMTkkvDl

If a sponsor has any other **EU exit queries related to customs procedures and tax**, HMRC can be emailed by externalstakeholders.customs@hmrc.gsi.gov.uk

8. Importing and Exporting tissues and cells, including biosamples

The Human Tissue (Quality and Safety for Human Application) Regulations 2007 transpose the EU Tissues and Cells Directive (EUTCD) in UK law.

Under these Regulations, the HTA regulates establishments that undertake the procurement, testing, processing, storage, distribution, import and export of tissues and cells for human use. This includes any steps involved in the handling of tissues and cells prior to them being manufactured into medicines.

In event of a 'no deal', the UK will become a third country for the purposes of the EU Tissues and Cells Directive. The UK will also consider EU Member States to be third countries.

Transport of tissues and cells from and to EU Member States will need to be covered by an appropriate import or export licence from the Human Tissue Authority (HTA). More information is available on the HTA website https://www.hta.gov.uk/guidance-professionals/eu-exit-updated-guidance-no-deal-preparations

We expect there to be limited impact on the movement of biosamples in a clinical trial context (i.e. blood or tissues removed for analysis purposes to provide data for a clinical trial) between the UK and the EU (other than potential transport disruption), as these samples are considered relevant material under the Human Tissue Act. For the purposes of the Human Tissue Act:

1. import and export is considered as into and out of England, Wales or Northern Ireland. This definition will be unchanged; and
2. import and export are not licensable activities under this legislation.

Biosamples are included in the DHSC Dedicated Shipment Channel discussed above.

9. Guidance on submitting MHRA clinical trials submissions, Developmental Safety Update Reports (DSURs)

On 11 March, the MHRA published *Clinical Trials – information Pack: How to submit to the MHRA in a EU no-deal scenario.* The pack provides answers to the following questions for both commercial and non-commercial clinical trails applicants:

- How to register to use MHRA Submissions
- How to enable other users in your organisation to submit via MHRA Submissions
- How to submit Clinical Trials Submissions via MHRA Submission
- How to submit Developmental Safety Update Reports (DSURs) via the new system

https://www.gov.uk/guidance/regulating-medical-devices-in-the-event-of-a-no-deal-scenario#registrations

https://www.gov.uk/guidance/guidance-on-registration-of-clinical-trials-for-investigational-medicinal-products-and-publication-of-summary-results

If a sponsor has any questions regarding registration for MHRA Submissions; please email submissions@mhra.gov.uk

10. Import Licences for Investigational Medicinal Products

If the UK leaves the EU without an agreement, sponsors of clinical trials in the UK that source investigational medicinal products (IMPs) from an EEA State will need to review their existing supply chains.

If you are the sponsor of a clinical trial running in the UK using IMPs imported from countries on an 'approved country for import' list (initially, all EU and EEA countries) you will require a UK Manufacturing and Import Authorisation (MIA(IMP)) holder to put in place an assurance system to check these IMPs have been certified by a Qualified Person (QP) in a listed country, before release to the trial.

IMPs that have been QP certified in a listed country will not require recertification in the UK. The IMP supply chain from a country on the approved country list will allow direct supply to clinical investigator sites. There will be a one-year transition period following the date of the UK's exit from the EU to implement this guidance.

Additional information on the importation of Investigational Medicinal Products (IMP) from EEA to the UK in a no-deal scenario is available.

https://www.gov.uk/government/publications/guidance-on-importation-of-investigational-medicinal-products-from-approval-countries/importing-investigational-medicinal-products-imp-from-eea-to-uk

General queries to the MHRA

If a sponsor has any other queries concerning MHRA's remit on clinical trials, they should contact the MHRA Clinical Trials Unit on

- Telephone (weekdays 8:30-16:30): 020 3080 6456
- clintrialhelpline@mhra.gov.uk

11. Further guidance and other areas of interest

The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019

The no-deal Statutory Instrument covering clinical trials for medicines has successfully passed through the House of Commons and the House of Lords. This can now be signed and made by Secretary of State and will come into force on exit day of a no-deal scenario.
http://www.legislation.gov.uk/ukdsi/2019/9780111179116/introduction

Guidance on registration of clinical trials for investigational medicinal products and publication of summary results
https://www.gov.uk/guidance/guidance-on-registration-of-clinical-trials-for-investigational-medicinal-products-and-publication-of-summary-results

Further guidance on the regulation of medicines, medical devices and clinical trials and clinical investigations if there's no Brexit deal
https://www.gov.uk/government/publications/further-guidance-note-on-the-regulation-of-medicines-medical-devices-and-clinical-trials-if-theres-no-brexit-deal/further-guidance-note-on-the-regulation-of-medicines-medical-devices-and-clinical-trials-if-theres-no-brexit-deal

UK and Pan European trials
In a no deal scenario, the UK would require the sponsor or legal representative of a clinical trial to be in the UK or country on an approved country list which would initially include EU/EEA countries. The MHRA offers to discuss any issues with organisations directly via their helpline below:

- MHRA Clinical Trials Helpline: 020 3080 6456.

The EU's current position is that where trials are pan EU, sponsors or legal representatives must be based in the EU. There is more information on the European Commission website.
https://ec.europa.eu/info/sites/info/files/notice_to_stakeholders_brexit_clinical_trials_final.pdf

Guidance on registration of clinical trials for investigational medicinal products and publication of summary results in a no deal scenario
https://www.gov.uk/guidance/guidance-on-registration-of-clinical-trials-for-investigational-medicinal-products-and-publication-of-summary-results

Guidance from MHRA on regulating medicinal devices in a no deal scenario
https://www.gov.uk/guidance/regulating-medical-devices-in-the-event-of-a-no-deal-scenario#ce-marking-your-devices-and-conformity-assessment

Amendments to HRA approvals
The Health Research Authority has published guidance on the implications of a no-deal Brexit. It brings together information on make amendments to approvals, transferring research data between countries and clinical trial supplies.

https://www.hra.nhs.uk/about-us/news-updates/latest-guidance-implications-nodeal-brexit/