

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

It is Government Policy that the UK will be leaving the EU on 31st October 2019. The Department of Health and Social Care (DHSC) has several priorities for our EU Exit planning, one of which is for all patients to continue to have access to medicines and medical products when we leave the EU. The Department is doing everything appropriate to prepare for the UK to leave the EU on the 31st October. We are working with all our partners and our plans should ensure the supply of medicines and medical products remains uninterrupted.

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, biosamples, 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 National Supply Disruption Response (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 NSDR (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 and clinical investigations, become aware of any issues regarding supply, key contacts have been established, and are discussed in further detail in this document.

Summary of Key Contacts:

- **Queries or early intelligence on potential issues/concerns related to EU exit – DHSC Clinical Trials Disruption Response Group:**
ctcontingencyplanning@dhsc.gov.uk
- **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 24th October 2019)
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- **General queries to the MHRA:**
 - info@mhra.gov.uk
 - Telephone (weekdays 9:00-17:00): 020 3080 600
 - <https://www.gov.uk/guidance/contact-mhra>
- **Queries to MHRA on UK and Pan European clinical trials of medicines:**
 - Telephone (weekdays 8:30-16:30): 020 3080 6456
 - clintrialhelpline@mhra.gov.uk
- **Queries to MHRA on UK and Pan European clinical investigations of medical devices:**
 - devices.regulatory@mhra.gov.uk

Trial sites should contact the Chief Investigator 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**
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 chief investigator of the clinical trial or investigation, or through the organisation running the clinical trial/investigation e.g. CRO or CTU.

DHSC understands that 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 and clinical 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 assisted with gaining assurance from sponsors on the state of the preparedness and contingency planning for any possible disruptions to clinical trials and clinical investigations supplies.

While the DHSC is working very closely across government (including the devolved administrations) and with NHS England to limit any impact of the UK leaving the EU without a deal on clinical trials and clinical 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.

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. Government contingency planning and shipping routes between the EU and the UK

On 8th October 2019, DHSC's Chief Commercial Officer, Steve Oldfield, sent a letter to all suppliers of medicines and medical products updating all sponsors on the Government's contingency planning to help ensure the supply of medicines and medical products (including for clinical trials and clinical investigations) is uninterrupted in the event of the UK leaving the EU without a deal. This letter provided more operational details of several elements of these plans, including:

- NAO Report: "Exiting the EU: supplying the health and social care sectors"
- Government-secured freight capacity
- Department of Health and Social Care's Express Freight Service procurement
- How to register for the Government's contingent freight measures
- Trader readiness and additional measures to support industry.

The Government has procured Secured Freight Capacity from freight operators which will be sold at market rates to suppliers of medicines and medical goods, including supplies for clinical trials and clinical investigations. The Department has announced the routes and terminals available in a letter to all sponsors. Access to the freight capacity will be via tickets; there will be no 'turn up and go' access.

DHSC has procured an Express Freight Service to provide access to an end-to-end solution able to deliver small consignments on a 24 hour bases and a two to four day pallet delivery service. This is designed to be used only if suppliers' own contingency

measures encounter difficulties or there is an urgent need for specific medicines and medical products.

Suppliers will need to register online to be eligible for access to both the Government-secured freight capacity and Express Freight Service, regardless of whether they registered last time.

Suppliers should register at <https://ship.mixmove.io/registerfreightservice>.

DHSC has put in place a unit of customs specialists to advise medical suppliers on preparations for the new customs and border arrangements that will come into place from Day One if the UK leaves the EU without a deal.

This dedicated health trader readiness unit will support medical suppliers in preparing for border and customs changes, including working with companies to ensure they have the necessary customs paperwork in place.

Sponsors can contact the unit here: betraderready@dhsc.gov.uk

If a sponsor has not received this letter from Steve, the accompanying guidance or the subsequent link to register onto the portal, 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 and clinical investigation sponsors to ensure continued supplies for their clinical trial/investigation. Clinical trial and clinical 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 and clinical 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 clinical trial and clinical 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 chief investigator 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 and clinical investigation supplies, it is important that DHSC is prepared to respond to supply disruption incidents should they occur.

As part of its Operational Response Centre, the DHSC 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 Express Freight Service; 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.

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 date from 24th October 2019)**

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:

- 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-theres-no-brexit-deal/>

- 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/eu-exit/data/>
- 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 2018, 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 2018) 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 imports will continue to be available should the UK leave the EU without a deal.

The Government has brought together a set of guides about trading with the EU after October 31st.

<https://www.gov.uk/topic/business-tax/import-export>

This includes guidance on importing/exporting goods:

- Exporting - <https://www.gov.uk/prepare-export-from-uk-after-brexite>
- Importing - <https://www.gov.uk/prepare-import-to-uk-after-brexite>
- Further information on getting an Economic Operator Registration Identification (EORI) number- <https://www.gov.uk/eori>

If the UK leaves the EU without a deal, organisations importing/exporting clinical trial supplies, including biosamples will be required to follow the rules for importing/exporting goods from the rest of the world.

Importing: <https://www.gov.uk/starting-to-import/importing-from-noneu-countries>

Exporting: <https://www.gov.uk/starting-to-export/outside-eu>

Organisations importing/exporting clinical trial supplies, including biosamples, will also need to ensure the correct commodity codes are used and will need to declare goods imported into the UK by submitting a customs declaration. Further information can be found at:

<https://www.gov.uk/guidance/finding-commodity-codes-for-imports-or-exports>

<https://www.gov.uk/guidance/customs-procedures-if-the-uk-leaves-the-eu-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>

Customs procedure code information can be found at:

Imports: <https://www.gov.uk/government/publications/uk-trade-tariff-customs-procedure-codes/imports-aphabetical-index-of-customs-procedure-codes>

Exports: <https://www.gov.uk/government/publications/uk-trade-tariff-customs-procedure-codes/exports-aphabetical-index-of-customs-procedure-codes>

HM Revenue & Customs (HMRC) has also produced information videos about trading with the EU after October 31st, including:

- The webinar '*Getting ready for Brexit*' which covers 5 key areas UK businesses must be aware of to keep trading goods when the UK leaves the EU

<https://www.gov.uk/guidance/help-and-support-for-traders-if-the-uk-leaves-the-eu-with-no-deal>

8. Importing and Exporting tissues and cells, including biosamples

Importing and Exporting tissues and cells for human application (including starting material for ATMPs):

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-guidance>

This licensing requirement applies to the export of all tissues and cells intended for use in human application, including those that will be used in the manufacture of an advanced therapy medicinal product (ATMP) where the tissues and cells are referred to as starting materials.

Further information is available on the HTA website at: <https://www.hta.gov.uk/faqs-hta-licensing-requirements-human-tissues-and-cells-used-clinical-trials-and-medicines>

Importing and exporting biosamples for analysis:

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 Express Freight Service discussed above.

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

The MHRA has published guidance on how to make submissions in a no deal scenario. The guidance provides information to both commercial and non-commercial clinical trials applicants on:

- 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/making-submissions-to-the-mhra-in-a-no-deal-scenario>

<https://www.gov.uk/government/publications/how-to-make-regulatory-medicines-submissions-to-the-mhra-if-the-uk-leaves-the-eu-with-no-deal>

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 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.

This assurance system must be overseen by a UK QP, however 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 of medicines or clinical investigations of medical devices, they should contact the MHRA's;

- Clinical Trials Unit on:
 - Telephone (weekdays 8:30-16:30): 020 3080 6456
 - clintrialhelpline@mhra.gov.uk
- Clinical Investigations Unit at:
 - devices.regulatory@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 will come into force on exit day of a no-deal scenario.

<https://www.legislation.gov.uk/uksi/2019/744/contents/made>

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>

Guidance on clinical investigations

<https://www.gov.uk/guidance/regulating-medical-devices-in-the-event-of-a-no-deal-scenario#clinical-investigations-and-performance-evaluations>

Guidance on notifying MHRA about a clinical investigation for a medical device

<https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device>

Submission of clinical investigations of medical devices using the Integrated Research Application System (IRAS)

<https://www.myresearchproject.org.uk/Signin.aspx>

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-brex-it-deal/further-guidance-note-on-the-regulation-of-medicines-medical-devices-and-clinical-trials-if-theres-no-brex-it-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

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/>

A collection of further guidance provided by the BIA

<https://www.biabrexit.org/>