**Joint Research Management Office document submission checklist**

 **(Medicines and Healthcare products Regulatory Agency regulated Clinical Investigations of Medical Devices)**

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| **Chief Investigator (CI):** |  |
| **Study Title;**  |  | Integrated Research Application System (IRAS) number: |
| **Sponsor:** |  | **On National Institute for Health Research (NIHR) Portfolio?**  | **Y/N/Applied and pending approval** |
| **Device Manufacturer:** |  |
| **EDGE Number:** |  | Work tribe number: |  |
| **IRAS Number:**  |  | Costings Officer |  |
| **ReDA Number:** |  | Division or Institute & centre: |  |
| **Speciality:** |  |
| **Will Barts Health NHS Trust (Barts Health) be a site?**  | Yes/No If Yes specify locations |
| **Have you discussed with Governance team?** | Yes/No | If yes Insert name |
| **Have you discussed with Good Clinical Practice (GCP) team?** | Yes/No | If yes Insert name |
| **External vendors or collaborators:**  | *Please list:* |

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| --- | --- | --- | --- |
| **Document** | **Essential** | **Included in submission****Y/N** | **Comment** |
| IRAS form  | Essential |  | *Please insert date of draft saved*  |
| Cover letter to Research Ethics Council (REC)  | Essential |  |  |
| IRAS MHRA Devices Form | Essential |  |  |
| Covering letter to the Medicines and Healthcare products Regulatory Agency (MHRA) | Essential |  |  |
| Public database registration | Essential |  | Please provide registration number if completed or temp number and state where study will be registered. |
| Clinical Investigation Plan (CIP) | Essential |  |  |
| Participant Information Sheet(s) (PIS) | Essential |  |  |
| Consent form(s) | Essential |  |  |
| Scientific peer review | Essential |  |  |
| Departmental authorisation | Essential but can be supplied during review |  |  |
| Letter from statistician(or agreed equivalent) | Essential |  |  |
| Joint Research Management Office (JRMO)-completed costings | Essential |  |

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| *Only supply with Worktribe number.* |

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| Funding / Award letter | Essential |  |  |
| Curriculum Vitae of CI, statistician and UK PIs | Essential |  |  |
| Evidence of ISO14155 GCP training for CI and statistician  | Essential |  |  |
| Health Research Authority (HRA) Organisation In formation Document  | Essential |  |

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| *\*Not applicable for Barts Health sponsored studies with only Barts health as a site.* |

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| HRA SoECAT | Essential |  |  |
| MTA / Material Transfer agreement | If applicable |  |  |
| Validated questionnaire | Yes, if applicable |  |  |
| Non-validated questionnaire | Yes, if applicable |  |  |
| Interview topic guides | Yes, if applicable |  |  |
| Letters/emails of invitation to participants | Yes, if applicable |  |  |
| Letters and/or information sheets for GP/consultant | Yes, if applicable |  |  |
| Investigator’s Brochure (IB) | Yes |  |  |
| Sponsor Medical/Clinical physics approval | Essential |  |  |
| Sponsor Radiology approval | See guidance |  |  |
| Sponsor Pathology approval  | See guidance |  |  |
| Evidence of appropriate translation | See guidance |  |  |
| Device Details Document | Essential |  |  |
| Essential Requirements Checklist | Essential |  |  |
| Risk Analysis | Essential |  |  |
| Instructions for Use of Medical Device | Essential |  |  |
| Device Labels | Essential |  |  |
| Summary of all bench testing and pre-clinical testing conducted | Essential |  |  |
| Summary of all clinical experience with the device to date | Essential |  |  |
| List of standards met | Essential |  |  |
| End of study reports for any concluded clinical investigations that involved the same medical device under investigation | Essential |  |  |
| Sterilisation validation report | Where relevant |  |  |
| Software information | Where relevant |  |  |
| Biological safety assessments of patient contacting materials | Where relevant |  |  |
| Information on animal tissues | Where relevant |  |  |
| Information on any medicine or human blood derivative incorporated into the device | Where relevant |  |  |
| Active devices information | Where relevant |  |  |
| Specialist technologies information | See guidance |  |  |
| Active implants information | Where relevant |  |  |
| Any other documents you think would be relevant to the submission | See guidance |  |  |

Study submission documents should be sent to: research.governance@qmul.ac.uk, who will also be able to help with questions and queries.

**Guidance**

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| All documents that will be submitted to the MHRA, HRA and HRA should be submitted.All documents should be submitted in word format (editable format) and in draft. |
| IRAS form | Main application form that constitutes application to regulatory bodies found here: <https://www.myresearchproject.org.uk/> To be submitted for sponsorship in draft PDF. |
| Cover Letter to MHRA | Include: * Purpose of Clinical Investigation
* Whether investigation is First in Human, Pilot/Feasibility, Confirmatory or post-market.
* Whether study has commenced in other countries and global start and end dates.
* Whether device has been trialled in a clinical investigation before. If so, provide MHRA reference numbers and state whether any modifications have since been made to the device.
* Whether this or a similar investigation has been rejected by the MHRA or another competent authority, the grounds for objection and how the investigation has since been changed.
* If the study is post-market and taking place in Northern Ireland – state any invasive or burdensome procedures required by the CIP that are additional to the normal use of the device in clinical practice.
* Any declarations of conflicts of interest.
* Any individuals or institutions that you do not want to be involved in the review of the Clinical Investigation (the MHRA may sometimes contract external assessors to review elements of the investigation).
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| CIP template | The JRMO Clinical Investigation Plan (CIP) template (associated document 3) must be used unless a CTU is involved and using their agreed template or there are exceptional circumstances. The CI must write a CIP that is in line with regulatory requirements.  See main SOP 9 for full guidance |
| PIS | For all studies that involve prospectively recruiting patients or healthy volunteers. Not applicable for some studies. HRA guidance available.If a multisite study, please submit without local headers so it can be adapted at each site. For single site, the documents should be localised to site. |
| Consent form(s) | For all studies that involve prospectively recruiting and consenting patients or healthy volunteers. Not applicable for some studies. HRA guidance available. If a multisite study, please submit without local headers so it can be adapted at each site. For single site, the documents should be localised to site. |
| Scientific peer review | Ideally external and independent review of the protocol. Supervisor review accepted for educational research. If external funding awarded this is accepted. Please include evidence that you have reviewed and implemented change suggestions or evidence of correspondence with review to justify why not.  |
| Departmental authorisation | Letter/email authorisation of appropriate person within the department in which the research will take place  |
| Letter from statistician  | This is to evidence statistician accountability and awareness for the statistical methods described in the Clinical Investigation plan.A standalone letter from the statistician is preferred but the MHRA has been known to accept a statistician’s signature on the CIP. NB If the statistician is external then a contract is required. |
| Researcher training certificate | [ISO](file:///C%3A/Users/GCP/AppData/Local/Microsoft/Windows/Temporary%20Internet%20Files/Content.Outlook/CHNVYMR4/ISO) 14155 GCP training is required – ICH GCP training will not be accepted. |
| Costings | Please see following link to the online costing questionnaire: <https://webapps2.is.qmul.ac.uk/ecosting/> If there are no costs a No Cost Declaration Form is to be completed.  |
| Curriculum Vitae  | Must be signed and dated.  |
| HRA Statement of Activities | Needed for multi-site studies. 1 form for each site *type*  |
| HRA Schedule of Events | Needed for multi-site studies. 1 form for each site *type.* Not applicable for Barts Health sponsored studies with only Barts Health as a site. [*https://www.nihr.ac.uk/documents/etc-soecat-guidance/11483*](https://www.nihr.ac.uk/documents/etc-soecat-guidance/11483) |
| Validated questionnaire | Evidence of the copyright |
| Investigator Brochure | This should normally be provided by the device manufacturer. See Annex B of ISO 14155 (available from the Queen Mary library) for the required content and layout. |
| Sponsor Medical physics approval | Mandatory for all Clinical Investigations.Please contact: research.clinicalphysics@nhs.net  |
| Sponsor Radiology approval | Needed when there is any imaging performed with in the CIP. Please contact: bartshealth.researchimaging@nhs.netTo initiate the local imaging review please forward the following: IRAS, Protocol, PIS, and Imaging Manual (if available) |
| Sponsor Pathology approval  | Needed when Barts Health pathology will act as a central facility or a blood product is in use (Provisional approval initially required). Please contact: bartshealth.ResearchPathology@nhs.net |
| Lung function testing | Please contact paul.pfeffer1@nhs.net and andy.stubbington1@nhs.net where there is a requirement for lung function testing at Barts Health.  |
| Evidence of appropriate translation | It may be necessary to translate some of your study documents in order to open the study in other countries, or to recruit participant groups who do not speak English. Translated documents must be accompanied by:* A translation certificate or other suitable evidence from the organisation completing the translation.
* Back-translation evidencing that the meaning of the text has not changed.

Any translated materials that will be given to participants must also be submitted to, and approved by, the REC.The study team should discuss the proposed method of translation with the JRMO to confirm its suitability. The translation service will be considered a vendor and must undergo JRMO contract and vendor assessment processes. |
| Medical Device Documents - The below documents should normally be provided by the device manufacturer, the guidance presented here is for the study team’s information. Guidance on these documents provided below is from the MHRA document “Clinical Investigations of medical devices – compiling a submission to the MHRA: <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/780236/Guidance_for_mfrs_-_compiling_a_submission_to_MHRA.pdf> |
| Device Details Document | The depth of detailed information supplied with the notification should be appropriate to the classification of the device, novelty of design, materials used and risks associated with the device. * Detailed description of device, how the device is assembled and how the constituent parts are joined together.
* A list of accessories, principles of operation and block or flow diagram of major components.
* Principal design drawings and circuit diagrams, together with a description and explanations necessary for the understanding of the said drawings and diagrams.
* A picture or schematic illustration of the device operation and photos of the device.
* A video demonstrating the operation of the device if available.
* For device systems provide a summary of how compatibility of all device components (whether UKCA/CE UKNI/CE marked or not) has been determined, including an updated risk analysis covering this.
* For UKCA/CE UKNI/CE marked devices being used for a new intended purpose that is not covered by the existing UKCA/CE UKNI/CE marking please provide full details of the new intended use and how this compares to the original intended use.-
* For UKCA/CE UKNI/CE marked devices being used as ‘ancillary’ devices within the study: MHRA Guidance on legislation Clinical investigations of medical devices 11/16 ‐ Ensure the devices are being used in accordance with the UKCA/CE UKNI/CE marked instructions for use; ‐ Provide evidence that the safety profile of such devices has been assessed to ensure there are no current safety concerns. This assessment should, as a basic step, involve a search of any safety notices published by the manufacturer or MHRA.
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| Essential Requirements Checklist | * Essential Requirements / General Safety and Performance Requirements checklist detailing how these requirements have been addressed, including references to designated or harmonised standards as appropriate.
* Include evidence of how applicable standards have been met.
* Include copies of all test reports and other documents referenced in the checklist within the submission to MHRA
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| Risk Analysis | * Provide a risk analysis preferably to EN ISO 14971:2019.
* For device systems the risk analysis should cover compatibility of all device components (whether UKCA/CE UKNI/CE marked or not).
* For devices incorporating an ancillary medicinal substance the risk analysis should cover compatibility between the medicine and the device materials
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| Instructions for Use of Medical Devices | Required for all investigational device components. Should include where relevant, information on setup of the equipment for use with a patient and any pre-use checks that may be required |
| Device Labels | Copies of the labels for the investigational device (the wording should state that the device is ‘Exclusively for clinical investigations’) |
| Summary of all bench testing and pre-clinical testing conducted | * A summary of all bench testing conducted, the results obtained and the manufacturer’s conclusions with details of which device model and version was involved. Include a justification for choice of each bench test performed, reference to the specific standard where the test is stipulated (where relevant) and whether the test has been adapted in any way.
* Where equivalence is claimed, provision of supporting data should cover the clinical, technical and biological aspects of the device in line with MEDDEV 2.7.1
* Results of design calculations
* Acceptance criteria for testing e.g. tensile strength and stiffness
* Confirmation of whether each device will be individually tested for conformance to the design criteria after manufacture
* a summary of all testing conducted in animals or ex vivo, the results obtained and the manufacturer’s conclusions. Include a justification for the number and species of animals used and any non-animal models tested. For implantable devices include detail on the condition and integrity of the device at explant and histopathological results. Studies conducted should be in accordance with ISO 10993.
* a summary of any testing conducted to address human factors and usability engineering. See MHRA guidance on Human Factors and Usability Engineering.
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| Summary of all clinical experience with the device to date | This should include adverse events seen and performance related complaints, including number of complaints of each type and the root cause in each case. Confirmation of whether the device involved was identical to the investigational device intended to be used in the proposed clinical investigation. If not, provide full details of how the new device differs. Detail changes to the design, materials, intended use and the rationale for these changes. Provide information on all First In Human and Pivotal Trials, irrespective of the place and time of the study and the results. |
| List of standards met | * list of all designated or harmonised standards that the device complies with including year of issue.
* If the standard(s) are only met in part, please provide a description of solutions adopted to meet the essential requirements of the UK MDR or general safety and performance requirements listed in Annex I of the EU MDR.
* Provide a full justification for where the standards met have been superseded
* Note: The application of designated or harmonised standards is voluntary and applicants may choose alternative methods of demonstrating compliance with the essential requirements. For example, compliance with international, national or in-house standards. Please provide a full justification where such alternative methods have been chosen.
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| End of study reports for any concluded clinical investigations that involved the same medical device under investigation | Contact the device manufacturer and sponsor to check whether they have any End of Study reports from previous investigations. |
| Sterilisation validation report | If the investigational devices are sterilised, the following information should be provided: * the method of sterilisation
* details of the sterilisation facility, name, location, process
* details of the records for product release (indicator testing, dosimetric release, parametric release), this should include the results and outcomes
* details of any standards applied to the any of the sterilisation processes.
* A sterilisation validation report for each component including:
* Proof of sterilisation validation protocols and processes to demonstrate that the sterilisation process can be delivered effectively and reproducibly to the specified devices in the sterilisation load, e.g. validated results, certificates, standards, risk assessments, and justification for the choice of sterilisation process MHRA Guidance on legislation Clinical investigations of medical devices 13/16
* Details of appropriate methods for bioburden determinations e.g. type (nature), frequency, results and outcome;
* Details of microbiological environmental precautions undertaken on the devices during manufacture or sterilisation e.g. type of controls, frequency of monitoring, results and outcome.

If devices are to be sterilised at the point of use, the following information should be included where appropriate: * a copy of the instructions for decontamination (i.e. cleaning, disinfection and or sterilisation) including details of any special precautions for handling
* appropriate validation data to demonstrate that the processes can be delivered effectively and reproducibly to the specified devices must be provided.

Where devices are sterilised at the point of use, and moist heat (steam) is chosen as the method of sterilisation, particular attention should be taken with regards to the ‘standard sterilisation parameters’ applicable within the country where the devices are to be processed and sterilised. The appropriate sterilisation qualification and validation reports should take account of these ‘standard’ requirements:* specification of manufacturing environment used
* details of any cleaning process prior to sterilisation
* method of sterilisation
* parameters of the sterilisation process
* site(s) of sterilisation (if different from manufacturing site(s))
* packaging materials used
* summary of sterilisation validation data
* details of routine monitoring of the sterilisation process.
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| Software information | For medical devices that include a software component (either stand-alone software or software incorporated into a medical device) the following should be addressed in the notification: Please provide copies of all documents referenced in the answers given to the software questions in the Clinical Investigation Application form.Please provide documentation to demonstrate that the software has been developed in accordance with its safety classification. At a minimum the following is necessary:* Software Development Plan
* Risk Management Plan and Report – specifically including the software hazard analysis.
* Software Configuration Management Plan
* Software System Requirements Specification
* Software System Verification Plan and Report
* Documented Software Problem Resolution Process.
* Evidence of review of completeness for software release

For stand-alone software, please ensure the whole system is considered and hazards caused by the platform/hardware the software is run on are addressed. |
| Biological safety assessments of patient contacting materials | Required for all investigational devices that are patient contacting:* Detailed description of how biocompatibility and biological safety have been addressed.
* The risk assessment should cover the rationale for the decisions adopted. It should be apparent from the risk assessment, how hazards were identified and characterised and how the risks arising from the identified hazards were estimated and justified in relation to anticipated benefits.
* Particular attention should be paid to biological safety issues, especially for devices containing new materials that will come into contact with patients or where established materials are used in a situation involving a greater degree of patient contact. For example, where particularly hazardous materials may be present in the final device, the risk assessment should indicate why solutions avoiding the hazard have not been adopted.
* A description of how the biological safety of the device has been evaluated should be included. This should include the identity of the person(s) responsible for the risk assessment, a summary of the data examined and the basis for the judgement that the materials are suitable for the proposed use.
* Information sufficient to characterise fully the identity and chemical composition of all materials coming into patient contact, including name and address of manufacturer, trade name/code, quantitative formulations, results of chemical analyses, assessments of the effects of sterilisation or other processes, or other data as appropriate, should be included.
* Haemocompatibility risk assessment (all endpoints should be considered including haemolysis, thrombosis, coagulation, platelet activation and the working of the complement system).
* Please refer to MHRA guidance on biological safety assessment for further details.
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| Information on animal tissue | For medical devices incorporating tissues of animal origin the following information should be provided: * A clear, justified statement on the decision to use animal tissues or derivatives, the expected clinical benefit, the evaluation of similar materials of animal origin and other synthetic alternatives that achieve the desired product characteristics and intended purpose.
* An overview and assessment of the key elements adopted in the risk management to minimise the risk of infection including the:
* availability of suitable alternatives
* selection procedures and systems for sourcing the tissue / derivative - details of the production processes and animals used
* source country including the assessment of geographical risk
* nature of the starting materials
* systems for inactivation or removal of transmissible agents and validation of these
* any other risk management measures that have been applied to reduce the risk of infection
* quantity of animal starting tissues or derivatives required to produce one unit of medical device
* tissues or derivatives of animal origin coming into contact with the patients and users, and the route of application
* practices of post-market surveillance system including gathering and assessment of new information of the potential risks arising from the use of the end product.
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| Information on any medicine or human blood derivative incorporated into the device | * Intended purpose of the inclusion of the medicinal substance in the context of the device and the risk analysis.
* Source, marketing authorisation (where applicable) and the quantity/ dosage of the medicinal substance, incorporated into the device.
* Method of manufacture (solvents/reagents used in processing, residuals).
* Qualitative and quantitative tests carried out on the medicinal substance in the device.
* Stability data in relation to the expected shelf-life/ lifetime of the device. Patient information regarding storage of the device should be included.
* Clinical documentation (clinical data demonstrating the usefulness of the medicinal substance).

Additional information required with regard to the medicinal substance only:* Control of the medicinal substance - medicinal substance specifications e.g. summary of the European Drug Master File, EDQM Certificate of Suitability, reference to European Pharmacopoeia or national monograph of a European Member State. - Manufacturers may wish to cross-reference a granted Clinical Trial Authorisation (CTA). - Please refer to ‘The rules governing Medical Products in the European Community’ volume III, Addendum II.
* Toxicological profile (summary of results of toxicity testing / biological compatibility). - This should include the effect on reproductivity, embryo/fetal and perinatal toxicity and the mutagenic / carcinogenic potential of the medicinal substance.
* Pharmacodynamics of the medicinal substance in relation to the device.
* Pharmacokinetic characteristics (local/ systemic exposure patterns, duration and maximum exposure and the maximum plasma concentration peak taking into account individual variability). - active substances should address the release of the substance from the device, its subsequent distribution and elimination.
* Local tolerance (particularly where the route of exposure is different to the conventional application) e.g. the results of EN/ISO 10993 testing, or a review of scientific literature.

Additional information required with regard to the human blood derivative only: * Control of the human blood derivative
* control of plasma source e.g. summary of the European Plasma Master File, - production of the blood derivative
* Manufacturers may wish to cross-reference a granted Clinical Trial Authorisation (CTA) or marketing authorisation for a medicinal product.
* Pharmacodynamics of the human blood derivative in relation to the device
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| Active Devices information | The device details or summary of all bench testing and pre-clinical testing should include:* Documentary evidence supporting compliance with any of the standards referenced. This may include certification by an independent body, or test house. Alternatively, self-certification is acceptable, providing this is supported with evidence of design input and subsequent in-house verification.
* For those applicants choosing self-certification against EN 60601-1 (which includes protection against electric shock hazards, mechanical hazards, fault conditions, constructional requirements, etc) a checklist for that standard, or equivalent, should be provided. This should be completed and signed by a competent engineer. Where clauses are considered not applicable, a justification should be given. Where measurements of leakage currents are made, the values should be recorded.
* When the medical device is to be used with other devices as part of a system, e.g. connection to laptop computers, etc an additional EN 60601-1-1 checklist or equivalent covering the whole system under investigation should also be provided.
* Details (with diagrams) of: how the battery is sited within the device, the earthing to ensure patient-user safety, earth leakage current, whether the devices incorporate electrical and thermal fuses, battery consumption indicator, audible/visual low battery alert, audible/visual battery error alert, other audible/visual error alerts.
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| Specialist technologies information | Includes: infra-red, laser, microwave, MRI, RF ultrasound, ultraviolet, X-ray etc. The device details or summary of all bench testing and pre-clinical testing should include details of how this technology has been incorporated in the design and what steps have been taken to assure the safe application in the device. Information pertaining to output power, justification of safety limits used and reference to appropriate standards should be included, e.g. the relevant part 2 of the EN 60601 series. |
| Active Implants Information | The device details or summary of all bench testing and pre-clinical testing should include:* A summary of the Failure Mode, Effects [and Criticality] Analysis (FMEA/FMECA).
* The results of animal studies.
* Performance statistics and adverse incident data of earlier model, when device is the next generation of an earlier design
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