Medical Device translation; from prototype to adopted product

Guidance document for PIs
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Objective:

• Provide a workflow summarising key activities and considerations for design, development, evaluation and commercialisation of Medical Devices*, to facilitate their effective translation into the clinic

*Medical Devices as defined by the Medical Device Regulation (MDR; published May 2017), this does not include in vitro diagnostics: https://www.gov.uk/guidance/medical-devices-eu-regulations-for-mdr-and-ivdr
Considerations

- Device Development Team
- Design & Development
- Laboratory / Pre-clinical Evaluation
- Manufacturing a clinical prototype
- Clinical Evaluation
- Commercial adoption
Device Development Team

- Successful translation of an idea into a NHS-adopted medical device is reliant upon the consideration & effective decision-making of a diverse group of individuals.

- The input from experts **throughout** the product’s development path is essential and a ‘Development Team’ should be formalised early, including key members & responsibilities:

<table>
<thead>
<tr>
<th>Chair</th>
<th>Project Management</th>
<th>Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human factors</td>
<td>Health Economics</td>
<td>Patient &amp; Public</td>
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<td>Clinical</td>
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- The Team should meet regularly to ensure continuous review of progress, awareness & relevance to the clinical and competitor landscapes and to ensure **decisive project advancement**.
IDEA:

- **Target Product Profile (TPP)** – captures the ‘benefit’ of the proposed medical device and key considerations in the strategic development of the product (incl. technical, scientific and medical information required to satisfy regulators and industry partners)

**TPP headings**

- Intended use
  - *Indications, target patients, operators, clinical setting?*
- Device description
  - *Predicate devices, needs (e.g. accessories, software)?*
- Contraindications
  - *Settings where risk of medical device outweigh benefit?*
- Non-clinical testing
  - *Sterility, biocompatibility, robustness, impact of failure?*
- Clinical testing
  - *Relevant safety & efficacy end points, health economics?*

**Longer-term considerations for Adoption**

- Intended use
  - ‘Unidentified’ opportunities for clinical benefit/use (e.g. arising from creative discussion with expanded audience)?
- Device description
  - *Ergonomics / ease of use*
- Contraindications
  - *Destined for stand alone use or routine employment alongside/in combination (e.g. consider comorbidities)?*
- Testing
  - *Usability testing assumes device is used as ‘imagined’*
    - Replicate/engineer testing in ‘work as done’ context
    - Design in ‘Resilience’ (i.e. minimum service adaption to enable adoption and diffusion, regardless of context)
UNMET CLINICAL NEED:

• As part of the TPP, comprehensively research and define the potential for benefit of the proposed medical device over current ‘standard of care’

• Understand the patient and clinician ‘pull’ – are they clearly aligned or conflicted?

INTELLECTUAL PROPERTY:

• Engage with Business experts (i.e. UCLB) to ascertain if you have a novel invention, ensure freedom to operate and to protect foreground/arising intellectual property

• All researchers with potentially commercialisable research results should fill out a confidential Invention Disclosure form (IDF) and submit it to their UCLB Business Manager: http://www.uclb.com/for-researchers/do-you-believe-you-have-a-novel-invention/
Regulators require that a formal methodology (i.e. Design Control) be applied to the conduct of medical device design & development.

EU and US processes are very much aligned (Section 7.3 of ISO 13485 2016; FDA 21 CFR 820.30 respectfully).
ISO 13485, Medical devices – Quality management systems – Requirements for regulatory purposes, is an internationally agreed standard that sets out the requirements for a quality management system to standardize the documentation process (e.g. approval and review, version control, availability).

Hospital in-house development is now covered by MDR (May 17-20), therefore requiring appropriate QMS, although it remains unclear where in-house academic devices fall since these technically do not constitute institutes treating patients.

**MEDICAL DEVICE QMS AT UCL:**

- Dept. medical Physics & Biomedical Engineering operates to ISO 13485 for medical software
- UCLH is operating to ISO 9001 and plans to migrate to ISO 13485 late in 2018
- The UCL Device & Diagnostics therapeutic innovation network (TIN) is working to support project teams in understanding and meeting regulation requirements for Device development (including the establishment of an appropriate QMS and document templates for device projects)
The Device & Diagnostics TIN is implementing a lean QMS to meet the basic regulatory requirements at the early stage of medical device development (i.e. ISO 13485-aligned)

The QMS does not provide the documentation required, only the processes needed to be followed to deliver the required documentation (incl. review, approval, version control, access, design & decision traceability)

It is necessary to keep and update records throughout the entire lifetime of the device, *It is not something that can be done at a later date, when ready for regulatory submission*

### Design History File / Technical File may comprise documents detailing:

<table>
<thead>
<tr>
<th>Document Type</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Specification</td>
<td>Design History File / Technical File</td>
</tr>
<tr>
<td>Device Classification</td>
<td></td>
</tr>
<tr>
<td>Preventative Actions</td>
<td></td>
</tr>
<tr>
<td>Risk Analysis &amp; Management</td>
<td>Essential Requirements Checklist</td>
</tr>
<tr>
<td>Quality Plan</td>
<td></td>
</tr>
<tr>
<td>Instructions for Use</td>
<td>Development Plans</td>
</tr>
<tr>
<td>Labels</td>
<td></td>
</tr>
<tr>
<td>Electronics Design</td>
<td>Verification</td>
</tr>
<tr>
<td>Software Design &amp; Architecture</td>
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<tr>
<td>Clinical Evaluation</td>
<td>Post-Market Surveillance</td>
</tr>
<tr>
<td>Major Subcontractors &amp; Agreements</td>
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</table>
DIFFERENT DOCUMENTATION TERMINOLOGY

• DESIGN HISTORY FILE
  – Design control documentation, demonstrating design verification and product safety evaluation (e.g. ISO 10993 Biocompatibility).
  – Documents the design and development process

• 510K SUBMISSION (US approval)
  – Following-on from the DHF, this document is commonly employed for FDA-approval of next-generation Class II devices (i.e. new devices with established precedents in that therapeutic arena)

• TECHNICAL FILE (EU approval)
  – Like the 510K, this captures design verification but additionally design validation data including clinical evaluation

• SUMMARY TECHNICAL DOCUMENTATION – STED
  – Resembles EU Tech File; preferred submission format for some markets
PROTOTYPE:

- Target Product Profile (TPP) – captures the ‘benefit’ of the proposed medical device and key considerations in the strategic development of the product (incl. technical, scientific and medical information required to satisfy regulators and industry partners)
- ISO 14971, Application of Risk Management to Medical Devices – An international standard for the requirements for risk management to determine the safety of a medical device by the manufacturer during the product life cycle

EVALUATION:

- Does your research prototype match the TPP and meet all the essential safety & performance requirements?
- Prototype verification
- ‘In-house’ versus contracted, external GLP-testing?
- Scalable processes/considerations for ‘clinical’ manufacture?
- ‘De-bugging’; iterative user & operator enhancements?
SOFTWARE EVALUATION:
ISO 12207, Systems and Software Engineering

- Test equipment requirements & engineer competencies?
- Software installation & testing
- Functional & User Test procedures
- Reliability & Performance testing
- Reporting & software refinement
- Documentation

IMPLANT EVALUATION:
ISO 10993, Biocompatibility

- Selection of device material(s) according to TPP & manufacturing considerations
- Refinement of production scheme and determination of potential limits & issues
- Early identification of materials supply & suitable manufacturing partners
- In-house testing of device components (e.g. flow rates for tubes, scenario tests)
- Identification of pertinent ISO10993 requirements to be evaluated
In-house medical device registration:

- In most cases, the Joint Research Office (JRO) will support and oversee investigator-initiated, clinical evaluation of in-house medical device development programs at UCL:
  - http://www.ucl.ac.uk/jro/academic-clinical-trials/sponsorship-clinical-trials
  - http://www.ucl.ac.uk/jro/approvals/research-network-coordinators-contact

- Early engagement with the JRO is essential to facilitate timely:
  - Foreword planning for evaluations to satisfy the regulatory authorities (e.g. MHRA, EMA, FDA)
  - Development of appropriate clinical manufacturing and research agreements, in partnership with UCL Research Services, UCLB and the TRO
  - Application to Clinical Engineering for permissions for device studies in UCL’s partner hospitals

Patient Public Involvement:

- Does your device TPP and the ‘research prototype’ meet all of the needs expressed by frontline clinical care providers, patient and public contributors (PPI)?

- Modify the research prototype iteratively, based on their experience of use/exposure to it

- Early PPI engagement will help raise awareness of the device in development and potentially facilitate patient recruitment for subsequent clinical evaluation, possibly even financial investment

- Timely identification of future needs or opportunities (e.g. 2nd generation device, app plug-in)?
Manufacture of non-CE marked clinical trial product (CTP), intended for commercialisation

Device Manufacturer (e.g. UCL, UCLH, RFH, MEH)
- Responsibility for the design, manufacture, packaging and labelling of a product for clinical trial, regardless of whether these operations are carried out by themselves or on its behalf by a 3rd party

Contract Manufacturer
- Appointed by the Device Manufacturer to achieve & document the production of the CTP
- Operates under a ‘Contract Manufacturing Agreement (CMA)’ which defines CTP
- Under terms of ‘Technical Agreement’ which define quality assurance & regulatory requirements
- May themselves sub-contract tasks

Materials Supplier
- Certified provider of medical-grade materials for CTP manufacture
- Supplies to contract manufacturer under the terms of their CMA
When transitioning to the manufacture of a ‘clinical prototype’:

- Agreement as to which organisation shall be the legal ‘Device Manufacturer’
  - Simple ‘aid to recovery’ app might be ‘manufactured’ by company set-up and owned by PI at UCL
  - Complex ‘artificial organ’ likely to be outsourced in entirety to UCL-appointed device manufacturer
- If employing a contract manufacturing organisation (CMO), UCL Research Services and the JRO shall co-develop the Contract Manufacturing Agreement
- The JRO shall lead on the development of the Technical Agreement to ensure Good Manufacturing Practice (GMP) regulatory compliance (e.g. inspection of the CMO)
- If Device is progressed via a UCL spin-out then UCLB shall lead on all manufacturing agreements
- All CMOs will be required to provide technical documentation to legal manufacturer or its appointed delegate
- All documentation relating to manufacturer and suppliers shall be included in the medical device master file
Clinical Evaluation

- Unmet Clinical Need
- Intellectual Property
- PROTOTYPE
- Laboratory Evaluation
- CLINICAL TRIAL PRODUCT
- Manufacturing
- Finance
- PPI
- Clinical Evaluation
- DOCUMENTATION
- MEDICAL DEVICE
- CE-marking
- Sell-out
- License-out
- Spin-Out
- IDEA
- Regulatory Approvals

ADOPTION
Clinical Evaluation

STUDY DESIGN:

• Medical device manufacturers are required to conduct clinical evaluation (incl. literature review, trials) to compare a new device to standard of care practice, or established similar devices, for (pre-)market approval and adoption

• Undertake risk-benefit assessment of the new device under actual clinical conditions of use

• ISO 14155 Clinical investigation of medical devices for human subjects - Good clinical practice. An international standard for studies carried out in human subjects to assess the safety and performance of medical devices for regulatory purposes

FINANCE:

• Regardless of altruistic drivers, clinical evaluation of devices has significant costs that must be met

• The TRO supports UCL device developers in attracting and managing public, commercial, investor and philanthropic funding for clinical studies of devices, appropriately costed in partnership with the JRO

REGULATORY & ETHICAL COMPLIANCE:

• The JRO and TRO support device developers in:
  - Seeking local, national & international approvals for device evaluations in hospital(s)
  - Engaging with Regulators in advance to identify and address potential hurdles to authorisations
  - Ensuring rigorous compliance of UCL researchers and contractors with international standards
GOING TO MARKET:

- Having completed the primary clinical and performance evaluation, release of a new Medical device onto the market then requires manufacturers to:
  - Undertake further, post market surveillance of safety in the wider population
  - Establish Vendor chains for after-sales training and service provision, problem reporting, tracking distribution and implementing recall procedures if required.

- In practice, the resources required for such an undertaking are often beyond UCL and the Device would be expected to be commercially adopted:
  - **SELL-OUT:** Device sold in entirety for one-off deal to a company/device manufacturer
  - **LICENCED-OUT:** UCL retains the Device but grants license to company for marketing
  - **SPIN-OUT:** UCLB investment establishes a separate commercial entity to market the device

DOCUMENTATION:

- Although resource-intensive from the start, the development of a comprehensive Device master file unquestionably increases commercial attractiveness and value of a product to a potential buyer, since it avoids the need to ‘back-fill’ the history and results of the Device design, manufacture & testing.
The value of the CE Mark (or US equivalent 510K or PMA):

• “Having a patent on a device is effectively useless without a CE Mark”

• CE-marking is a declaration of conformity with the EU’s Medical Devices Directive (MDD) and is:
  - NOT a requirement for clinical trial/evaluation (NB. such evidence may be required for CE-marking)
  - A requirement to place a device on the market in the EU

• Devices are grouped by increasing risk, with increasing assessment requirements:
  – Class I  Provided non-sterile or do not have a measuring function (low risk)
  – Class I  Provided sterile and/or have a measuring function (low/medium risk)
  – Class IIa (medium risk)
  – Class IIb (medium/high risk)
  – Class III (high risk)

• Class I devices can be self-certified (i.e. manufacturer ensures compliance with all the relevant essential requirements of the Medical Device Directive (MDD) and provides written statement to this effect), the device can be CE marked and then placed on the market.

• Although not required to ISO13485 standard, an appropriate Quality Management System is required to develop and maintain a Class I device.

• CE mark holding demands continual effort (e.g. post-launch surveillance) and UCL usually defaults to an option with an external company holding the CE mark.
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<tr>
<th>Risk Class</th>
<th>Risk Description</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Class I basic (non-measuring, non-sterile)</td>
<td>Low</td>
<td>Reusable surgical instruments (e.g. forceps, scissors, scalpel to be sterilised locally); ECG electrodes; Beds; Wheelchairs</td>
</tr>
<tr>
<td>Class I measuring</td>
<td>Low</td>
<td>Stethoscope; Thermometer; Non-invasive blood pressure; Volumetric urine bag</td>
</tr>
<tr>
<td>Class I sterile</td>
<td>Low</td>
<td>Sterile dressing (non-medicated); Examination gloves (e.g. item is supplied sterile then discarded)</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Medium-Low</td>
<td>ECG machine (recording only); diagnostic ultrasonic equipment; Hypodermic needles (NB. invasive, but exception as used only transiently); Suction equipment; Fridge (blood)</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Medium-High</td>
<td>ECG machine (continuous - with alarms [e.g. ICU]); Infusion pumps; Invasive blood pressure, Ventilators; orthopaedic implants; Contraceptives; Haemodialysis machine; X-ray machines</td>
</tr>
<tr>
<td>Class III</td>
<td>High</td>
<td>Drug eluting cardiac stents; Heart valves; Ultrasound equipment for use in interventional cardiac procedures</td>
</tr>
<tr>
<td>Active Implantable Medical Device (AIMD)</td>
<td>High</td>
<td>Implantable pacemaker; Implantable defibrillator</td>
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</table>
UCL has implemented and is growing strategic platform partnerships to facilitate the accelerated development, commercialisation and adoption of its medical devices into the NHS.

UCL’s Translational Research Office (TRO) builds on an increasingly vibrant translational culture across the wider university community by providing integrated support for translational research and industrial partnerships: www.ucl.ac.uk/translational-research
DESIGN FOR MARKET:

• Continuously undertake internal and external stakeholder review of the Device:
  - The Device Development Group should meet regularly (at least every 6 months)
  - Ensure the identification and measurement of tangible data that will support adoption (e.g. outcomes meaningful to ward managers, hospital laboratory managers)

• Be mindful of the key ‘facets’ developed for successfully adopted devices:
  
  **FISCAL OPPORTUNITY**  
  - Clearly defined & attractive market potential

  **SYSTEM OPERATIONS**  
  - Awareness & solutions to operational challenges of delivering the healthcare

  **COMMUNICATION**  
  - Effective publicity of the device throughout its lifetime

  **HUMAN FACTORS**  
  - Minimized use-related hazards, risks & inconvenience wherever practically possible

  **PROOF**  
  - Provision of ‘work as done’ evidence (i.e. in both clinical & laboratory scenarios)

  **IPR**  
  - Secure intellectual property rights as early as possible, then drive for market adoption as soon as possible (do not delay by developing next device generation)
Key contacts for support

Joint Research Office
www.indigo-sandbox.ucl.ac.uk/jro/contact-us

Translational Research Office
www.ucl.ac.uk/translational-research/

Device & Diagnostics
Therapeutic Innovation Network
www.ucl.ac.uk/slms/ovph/TINs

Device Development Team

UCL Business
www.uclb.com/for-researchers/

UCL Partners
https://uclpartners.com/contact-us/

Research Services
www.ucl.ac.uk/finance/research/rs-contacts.php