

Unit 2: Ethics and Quality

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2.1 Clinical investigation of medical devices: why and when

Clinical investigation is the device world's clinical trial: a systematic study in human subjects undertaken to verify the safety and performance of a device used as intended. Not every device needs one, and knowing when it does is the first judgment of this unit. Where the essential principles can be demonstrated by bench testing, standards conformity and literature on equivalent devices, clinical evaluation may rest on that evidence, and most low class devices reach the market so. Investigation is required where the technology, the claim or the risk leaves a question only human use can answer: typically novel high risk implantables, devices whose performance claim is itself clinical, and cases where the existing literature does not cover the intended purpose. The ethical frame is the one MRA103T built: the Declaration of Helsinki and the ICH GCP tradition, adapted to devices by ISO 14155, because device investigations have features drug trials lack: the intervention may be a procedure as much as a product, blinding may be impossible where a surgeon must know the implant, the device may be permanently implanted so that withdrawal from the study does not withdraw the exposure, and the operator's learning curve is itself a variable. Ethics committee approval, informed consent and insurance and compensation arrangements are required before first enrolment, and the sponsor's duty to monitor safety runs through the investigation, with device deficiencies, the near misses of the device world, recorded alongside adverse events.

2.2 The clinical investigation plan

The **clinical investigation plan (CIP)** is the protocol of the device investigation, the document ISO 14155 requires to be written, approved and followed, and its contents mirror a drug protocol with device specific additions. It states the identification and description of the device, its intended purpose and the claims under test; the objectives and the design, endpoints, subject population and sample size with their justification; the risk analysis of the device and the justification for exposing subjects, drawn from the ISO 14971 file of section 2.5; the procedures, including any surgical technique, training of investigators and the handling of device deficiencies; monitoring, data management and statistical methods; the ethical apparatus, ethics committee approval, informed consent documents and provisions for vulnerable subjects; and the reporting machinery for adverse events and deviations, with the criteria for early termination. Two companions travel with it: the **investigator's brochure**, assembling everything known about the device, its bench and preclinical data and the experience to date, so the investigator can judge risk independently; and the clinical investigation report at the end, on which the clinical evaluation of the device is built. Read the CIP as the point where ethics, risk management and evidence meet: every element of it answers to one of the three.

2.3 ISO 14155: good clinical practice for device investigations

ISO 14155 is the good clinical practice standard for the clinical investigation of medical devices, the device counterpart of ICH E6 for drugs, and the syllabus cites its 2011 edition, the edition on which this teaching is based, noting that the current edition is ISO 14155:2020. Its principles restate the ethical core in device language: investigations are conducted in accordance with the Declaration of Helsinki; the rights, safety and well being of subjects prevail over science and society; the device information must justify the exposure; and the investigation follows the approved CIP under qualified investigators and medical oversight. Its

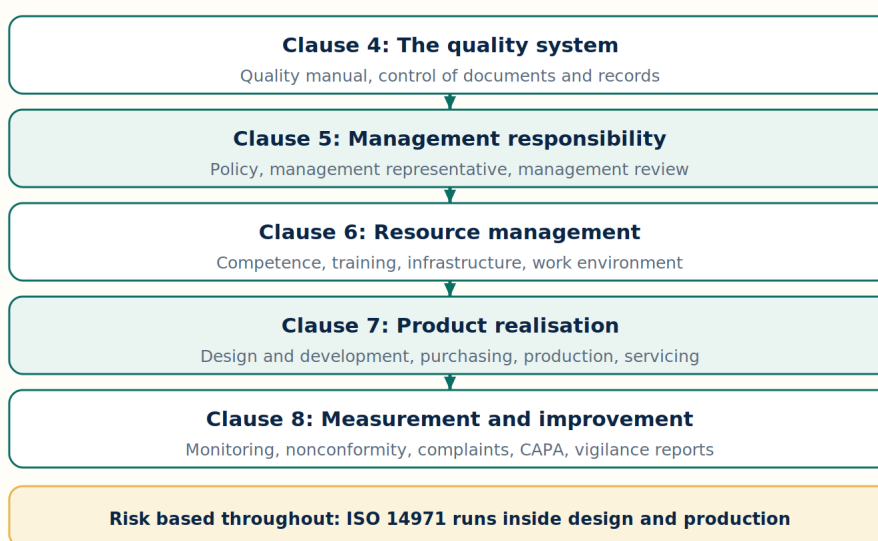
operative content is the allocation of duties. The **sponsor** designs and funds the investigation, selects and trains investigators, monitors conduct and data, manages device accountability and safety reporting, and owns the quality system within which the study runs. The **investigator** obtains ethics approval and informed consent, follows the plan, records data and deficiencies, and reports adverse events promptly. The **ethics committee** reviews the plan, the consent materials and the investigator's suitability, and keeps the investigation under review. What distinguishes the standard from its drug counterpart is its device furniture: device deficiency reporting (malfunctions and use errors that could have led to harm, reported even when no harm occurred), requirements on device accountability and traceability to each subject, and provisions for the learning curve and for investigations where the device cannot be removed. A clinical investigation run to ISO 14155 generates the clinical evidence that Units 3 to 5 then file in their several systems, which is why this unit precedes them.

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A device clinical investigation under ISO 14155
Bench, preclinical and risk file complete (ISO 14971)
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Clinical investigation plan written; investigator's brochure issued
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Ethics committee approval and regulatory notification or approval
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Informed consent of every subject before any procedure
|
Conduct: monitoring, device accountability, deficiency and
adverse event reporting throughout
|
Database lock and clinical investigation report
|
Clinical evaluation: the evidence enters the device dossier
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2.4 ISO 13485: the quality system regulation for devices

ISO 13485 is the quality management system standard written specifically for medical devices, the standard against which manufacturers worldwide are certified and the benchmark the quality items of this subject return to. It is built on the process architecture of ISO 9001 but diverges from it in the direction of regulation throughout: where ISO 9001 aims at customer satisfaction and continual improvement, ISO 13485 aims at **regulatory compliance and consistent safety and performance**, and it keeps requirements the general standard has relaxed, such as documented procedures, maintained records and controlled work environments wherever product quality demands them. Its clause map runs: the quality management system itself, with the quality manual and the control of documents and records; management responsibility, including the appointed management representative and management review; resource management, with competence, training and infrastructure; **product realisation**, the operative heart, covering planning, customer related processes, **design and development** with its inputs, outputs, review, verification, validation and transfer, purchasing and supplier control, production and service provision including cleanliness, installation and servicing, and the control of monitoring and measuring equipment; and measurement, analysis and improvement, covering monitoring of product and process, control of nonconforming product, complaint handling, reporting to regulatory authorities, internal audit and corrective and preventive action. Two ideas carry the examination weight. First, the standard is **risk based**: it calls up ISO 14971 risk management inside design and production, so the risk file of section 2.5 is a quality system document, not an annex. Second, in most jurisdictions certification to ISO 13485 by an accredited or designated body is the standing evidence that the quality limb of conformity is met, which makes the standard's audit, by a notified body in the EU scheme of Unit 4 or under the single audit programme of Unit 5, a market access event and not merely a quality exercise.

ISO 13485: the quality system in one view



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Figure: The ISO 13485 clause structure of section 2.4: management responsibility and resources around the product realisation core, design and development, purchasing, production and servicing, closed by measurement, complaint handling, vigilance reporting and CAPA (Unit 2, section 2.4).

2.5 ISO 14971: risk management for medical devices

ISO 14971 is the risk management standard for medical devices, and its process is the second language of this subject. The vocabulary first, because examinations test it precisely: a **hazard** is a potential source of harm; a **hazardous situation** is the circumstance in which people or property are exposed to the hazard; **harm** is the injury or damage that may result; and **risk** is the combination of the probability of the harm occurring and its severity. The process then runs as a disciplined cycle across the whole lifecycle. **Risk analysis**: the intended use and the characteristics related to safety are identified, hazards and foreseeable sequences of events are listed, and the risk of each hazardous situation is estimated. **Risk evaluation**: each estimated risk is judged against the acceptability criteria the manufacturer has set in advance in the risk management plan. **Risk control**: unacceptable risks are reduced, by the standard's ordered preference, first by inherent safety in design, then by protective measures in the device or its manufacture, and only last by information for safety, labelling and training; residual risks are weighed against benefit, and the overall residual risk is judged acceptable or not. **Production and post production activity**: the file stays open for the product's life, fed by complaints, vigilance and production data, and new hazards or changed estimates reopen the analysis. Everything is documented in the **risk management file**, which is the traceability spine from each hazard, through its controls, to the verification that the controls work. Risk management is not a department in this scheme: the clinical investigation plan of section 2.2 cites it, the design controls of ISO 13485 execute it, and the essential principles of Unit 1 are its acceptance test.

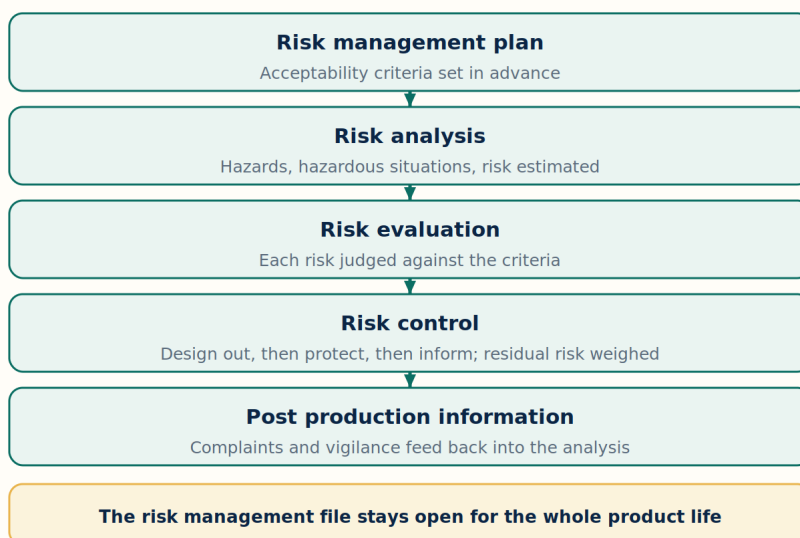
The ISO 14971 risk management cycle

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Risk management plan: acceptability criteria set in advance
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Risk analysis: hazards, hazardous situations, risk estimated
|
Risk evaluation: against the criteria
|
Risk control: design out, protect, inform (in that order);
residual risk weighed against benefit
|
Overall residual risk judged: acceptable or not
|
Production and post production information: complaints,
vigilance, production data feed back into the analysis
|
+---- the file stays open for the whole product life ----+

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The ISO 14971 risk management cycle



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Figure: The risk management cycle of section 2.5 as a loop: analysis, evaluation against criteria set in advance, control by design, protection and information in that order, and post production information feeding back, all documented in the risk management file (Unit 2, section 2.5).

2.6 Verification and validation of medical devices

The pair is a single examination favourite because the words are easily swapped and must not be.

Verification asks: did we build the device right? It confirms, by test, inspection, analysis or demonstration, that the design outputs meet the design inputs: the pump delivers the specified flow, the software responds within the specified time, the implant withstands the specified load, the sterilisation cycle achieves the specified sterility assurance. **Validation** asks: did we build the right device? It confirms that the finished device meets the user needs and the intended purpose in actual or simulated use: clinicians can operate it safely in the intended environment, the diagnostic result supports the intended decision, the implant performs in the body as claimed. Validation therefore reaches into usability engineering, the study of use error by the intended operator, and into clinical evaluation, where human evidence validates the clinical claims. Process validation stands beside the pair: where a process result cannot be fully verified by inspecting the product, sterilisation, moulding, aseptic sealing and software driven manufacture among them, the process itself must be validated, installed, operated and performance qualified, the qualification discipline met in MRA101T now applied to device lines. The three together are the engineering evidence on which the STED and every jurisdiction dossier of this subject rest, and design transfer, the controlled hand

over from design to production, is where they are audited.

2.7 Adverse event reporting of medical devices

Vigilance for devices follows the pattern of pharmacovigilance with device specific reporting objects, and the IMDRF adverse event terminology supplies the shared codes. The reportable core is the **incident**: an event in which a device malfunctioned or deteriorated in performance, a device's labelling or instructions proved inadequate, or a use error occurred, and the event caused, or could have caused, death or serious deterioration in health. The molecule of the device world is the **device deficiency**, the inadequacy of a device with respect to its identity, quality, durability, reliability, usability, safety or performance, including malfunctions, use errors and inadequate labelling; deficiencies are counted whether or not anyone was harmed, because in aggregate they are the leading indicator of the incidents to come. The manufacturer's duties run in channels: report incidents to the competent authority of the market concerned within the timelines that market sets, graded by seriousness; investigate, with the risk file of section 2.5 reopened by the finding; and execute **field safety corrective actions**, up to and including recall, with field safety notices informing users. Users and facilities report in parallel, and the aggregated data feed the post market surveillance of Unit 3. The professional point mirrors MRA202T's traceability lesson: a device report is usable only if it identifies the exact device, model, lot or serial and its UDI where assigned, which is why the identification machinery of the next unit is vigilance machinery too.

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