CORE-MD

Coordinating Research and Evidence for Medical Devices

An Ethics Charter for Innovation in Medical Devices

Deliverable 4.2

Deliverable factsheet

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1. Executive Summary

The most important function of a device regulatory process is to ensure that medical devices are fit for purpose in two ways: that they reliably perform the clinical function for which they are designed, and that they do not harm patients. The process of development, testing and regulatory approval of a device is complex and involves numerous stakeholders, and the necessary focus of these stakeholders on the technical requirements of the process has the potential to result in decisions which do not align with these high-level objectives. An ethical guide to the principles on which evaluation and decision-making should be conducted would be helpful in guiding stakeholders.

A consensus process, guided by professional ethical expertise, was developed in preliminary discussions among task members and at a workshop of the whole CORE-MD consortium, in order to provide such a guide for those working with the EU regulatory system to implement the Medical Device Regulation. The ethical framework adopted was based on the four accepted principles of medical ethics, namely beneficence, non-maleficence, autonomy, and justice. Added to this were a principle of maximum practicable transparency and a moderately strong precautionary principle. It was agreed that these principles should guide the behaviour of all stakeholders whether involved in developing, evaluating, or regulating devices, and that the current focus on the responsibilities of the device developer needs to be broadened to the other stakeholders.

The types of evaluation conducted during the development of a high-risk medical device evolve as more is learned about the device, and the ethical questions around the evidence requirements change accordingly. We therefore adopted a life-cycle based approach to considering ethical responsibilities. Using the IDEAL Framework as the basis for describing the evaluation life-cycle for devices, we considered three distinct phases – pre-market, pivotal, and post-market. We did not catalogue all responsibilities of all stakeholders, but consider that a more detailed description could be carried out to develop the Charter.

Each section in these summary proposals highlights what we think are the most important ethical requirements relevant to development, evaluation, and regulation during the relevant phase of the cycle. Some statements challenge current ways of working, which may imply the need to modify current processes, and some proposals may be inconvenient or costly. We welcome responses to this draft charter from national regulators, notified bodies, health technology assessment organisations, patients' associations, medical device manufacturers, EU policy makers in the field of medical devices, and clinical professional bodies at national and European levels.

2. Introduction: The need for an ethical charter for medical device regulation

The advances in medical technology of the last 50 years have resulted in the development of a huge number of devices intended to benefit human health – but which may also have the potential to cause harm. Where devices sub-serve a vital therapeutic or monitoring function, or are relied on for accurate diagnosis, malfunction can have tragic consequences. The process by which devices are developed is, of necessity, an iterative one which requires clinical evaluation, and this necessarily imposes a degree of risk on the patients or subjects involved. Regulatory frameworks have been developed internationally to reduce the risks of harm from medical devices and to ensure that we understand their benefits and costs. At the core of these frameworks is the ethical obligation to promote human wellbeing and avoid harm to individuals.

The issues involved are complex, as risks include not only direct harm to individuals but also matters such as injustice in access to treatment, societal "opportunity costs" imposed by expensive new treatments in systems with limited budgets, and conflicts of interest which may influence the behaviour of the parties involved. These include innovators and commercial device developers, clinical partners who test devices in practice, conformity assessment organisations (notified bodies), and national regulators; more indirectly research funding bodies, journal editors and publishers, and policy makers; and of course patients. Each stakeholder groups is faced with a different set of ethical questions and challenges, and interactions and relationships between the groups bring up additional ones.

The need for all parties in this field to act ethically is generally accepted, but this implies that there is an agreed ethical framework to which all subscribe, because if different parties interpret their ethical responsibilities in different ways, ethical behaviour becomes impossible to define. In addition, popular discussion of this subject usually places all of the attention on the responsibilities of the innovators and clinical partners, and assumes that the other parties are behaving ethically, or if not, that this is not important. When we reviewed the relevant existing ethical and legal frameworks we concluded that they did not address these two problems – the focus on innovators and the lack of a clear set of ethical principles fit for this purpose. We therefore determined that an "Ethical Charter" to guide the behaviour of all parties to the process of developing, evaluating and regulating medical devices would be helpful.

3. Brief description of the EU regulatory process and requirements for medical devices

Device developers are required to present evidence to a notified body in support of their application for a certificate of conformity, which leads to a CE mark and allows marketing of the device throughout the EU. The Medical Device Regulation requires that manufacturers conduct a clinical evaluation and there are some specific risks about which evidence of safety is required, covering aspects such as toxicity, teratogenic potential, and exposure to ionising radiation.

Medical devices are classified according to their perceived risks to patients from their use, and for higher-risk devices, direct clinical evidence is required to demonstrate safety and performance i.e. that the device does what it is supposed to do. The nature of the clinical evidence required is not specified in terms of methodology, and unless the results of investigations are published in the scientific literature, the actual studies done and their outcomes may be covered by commercial confidentiality agreements between notified bodies and innovators. They are then inaccessible except to competent authorities (national regulators), who can only request them in response to alert notices suggesting a risk of harm to patients. Notified bodies are prohibited from 'consultancy' with clients, which effectively prevents them from giving advice on study designs and on the type of evidence which would be most useful in demonstrating conformity.

Considering this general structure of the EU regulatory system, the members of this CORE–MD Task (4.1) and the participants in the consensus workshop listed the following groups as the most important participants in the whole process:

1 Device developers and innovators

2 Clinical investigators and trialists

3 Manufacturers including SMEs and start-ups

4 Ethics Committees

5 Notified bodies and regulatory authorities

6 Reviewers, editors, publishers of clinical research

7 Health technology assessment agencies

8 Physicians and healthcare professionals not involved in formal investigations

9 Patients

10 Policy Makers

Ethical guidance could be useful for all these groups.

4. Process of development of the Charter

The concept of preparing a Charter arose from discussions within the CORE–MD consortium about the multiplicity of actors in the regulatory system for medical devices, and the difficulty of harmonising the very different aims and perspectives of the stakeholder groups. The need to act ethically was identified as one of the few unifying principles which brought all stakeholders together, which therefore could serve as a powerful force for promoting consensus about evaluations and approvals should be conducted. Alongside methodological rigour and the avoidance of waste, ethical behaviour was recognised as a key principle which underpins clinical research and investigation.

The IDEAL Collaboration, partners in Work Package 2 of the CORE–MD project (as UOXF), were asked to leverage their previous experience of developing principles-based proposals for consensus guidelines to produce a draft document with assistance from a group of philosophers and ethicists with a special interest in the ethics of innovation in surgery and invasive medical treatments. The draft was then disseminated and debated at a CORE–MD group consensus meeting in November 2023 which included independent ethicists, experts in the EU regulatory process and representatives of patients. Modifications and additions to the draft document were made which reflected the conclusions of this meeting and a final draft was circulated among CORE–MD members for approval.

It was recognised, considering the complexity of the task, that it would benefit from having documents available that summarise the most important legal and ethical considerations and principles. These will be used as the background for preparing a manuscript for submission for publication, and they can be made available on request.

The ethical challenges were considered systematically by dividing the life-cycle of device development and evaluation into three phases – Pre-market development and evaluation, Pivotal studies, and Post-market evaluation, as the main problems which arise in these different phases are often quite distinct. To ease the task of the working group, we used the existing IDEAL-D framework to further subdivide the three phases.

The programme for the CORE–MD Ethics Workshop is shown in Figures 1 and 2.

CORE-MD Workshop: preparation of Ethics Charter for Medical Device Innovation

ESC office, 34 Rue de la Loi, Brussels / hybrid meeting

Monday 20th November 2023

11.00 Introduction and objectives
11.05 Setting the scene – ethical challenges and need for guidance

Learning from past experience
introduced by Peter Wilmshurst, and Sven Oven Hansson (KTH Stockholm)
- For investigators and collaborators
- Transparency and publication
- Responsibilities of manufacturers

CORE–MD summaries of existing regulations, guidance and standards
introduced by Janos Meszaros (KUL) and Drew Plath (Oxford)
- Legal and professional

Questions and discussion

13.00 Lunch

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Figure 1. Programme for Workshop on the Ethics Charter (part 1)

14.00 Discussion groups
By ethical principles (beneficence, non-maleficence, autonomy, and justice)
– from idea to prototype to feasibility and safety studies
– for clinical studies and trials, and dissemination
– during implementation into clinical practice and post-market surveillance

15.00 Break

15.30 – 15.45 Summary of discussions
15.30 – 18.00 Consideration of recommendations (chairs: Fraser/McCulloch)
By stakeholder community / stage of investigations in life-cycle
1. Developers and innovators
2. Investigators and trialists
3. Manufacturers including SMEs and start-ups
4. Ethics Committees
5. Notified bodies and regulatory authorities
6. Reviewers, editors, publishers
7. Health technology assessment agencies
8. Physicians and healthcare professionals

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Figure 2. Programme for Workshop on the Ethics Charter (part 2)

5. Ethical Framework Adopted

The consensus group accepted the proposal that the ethical framework should be based on the widely accepted four principles of medical ethics – beneficence, non-maleficence, autonomy, and justice.

To these were added the principle of maximum feasible transparency, both with respect to making study methods and outcomes publicly available and to communicating between the different stakeholders, particularly clinicians and patients. The assumption first proposed was that innovators should disclose all technical and clinical details about their devices and the outcomes of tests on them, except where this would expose critical aspects of their intellectual property to competitors.

The final principle accepted was a “moderate” precautionary principle. This requires investigators to pro-actively evaluate any clearly identifiable or predictable sources of risk to patients, based on existing theory and knowledge of the device and its expected use, but not to conduct exhaustive studies to exclude risks where there was no clear rationale for concern.

6. Ethical requirements for the pre-market phase

The recommendations listed here were selected on the basis of their perceived importance in the ethical framework underpinning the system for evaluating and licensing devices. These perceptions are specific to a particular point in time, and this list will therefore require regular review and revision. Although our stakeholder group was broad, all such groups will have unique characteristics which emerge from the way in which the specific stakeholders interact. Other groups may therefore differ somewhat in their emphasis, although hopefully not in a fundamental way.

Pre-clinical studies (IDEAL-D Stage 0)

- Innovators should be required to justify the development of their device, based on the existence of an unmet need, a strong economic case (such as equivalent effectiveness to existing technology at reduced cost) or an argument based on justice in access to treatment.
- The nature of the device, the materials used in it and the overall mode of action should be made available in the public domain, including a list of any IP protected by patents.
- Access to the description of the intended use of the device and the patient groups for which it is indicated should be easy.
- A risk analysis based on the mechanism of action of the device and intended use of the device should be conducted and made available for public scrutiny.
- An account of the tests carried out in preparation for licensing and their results, should be made available to the public in a searchable database or archive, including the risk analysis and the tests carried out in response to it (the last to be released only after CE marking).
- Full disclosure of conflicts of interest by innovators and clinical investigators should be obligatory, and should be made searchable and publicly available.

First-in-Human Studies (IDEAL-D Stage 1)

- Adequate explanation should be provided to the appropriate ethical oversight body on the nature and purpose of the device, together with pre-clinical evidence to support expected benefits and show that all predictable risks have been mitigated.
- The selection criteria for the first human patient to undergo treatment with a new device should be based on beneficence (maximising the potential benefits) and maleficence (minimising the risks of harm), and should be clearly explained. Where the potential benefits are substantial, and cannot be achieved by other means, a significant risk of harm may be acceptable.

- Candidate patients for the first-in-human use of a device should receive detailed informed consent in a manner which avoids bias due to conflicts of interest, provides useful information about what is currently known about safety and effectiveness, explains what alternatives are available, and makes clear that in this situation it is impossible to estimate or predict all risks.
- A full account of the screening and selection procedures involved in selecting the initial patient should be published, including an account of patients considered and rejected, with explanations.
- A full description of the procedure for using the device (including implantation where relevant) and the clinical and technical outcomes measured, should be made available for review by peers, regulators, ethical supervision groups and others in all cases, including those in which first use was unsuccessful or harmful.
- To allow full disclosure of outcomes, policies and laws may need to be modified in order to ensure legal protection for innovators whose ethically conducted First-in-Human studies harm patients.
- Ethical oversight bodies should consider and weigh the implications and potential risks of withholding or delaying approval for first-in-human clinical studies against the risks to patients of proceeding with current proposals.

Early Clinical Studies (IDEAL-D Stage 2a)

- Since changes to devices, their indications and the manner in which they are used based on early clinical experience are common, early clinical studies should describe and explain such changes, their rationale and their outcomes fully. This should include transparent reporting of unsuccessful modifications, which will avoid their repetition by others.
- Regulatory frameworks should be designed to allow this kind of reporting of parallel early innovation and evaluation in a realistic manner until the device and its implantation and use achieve a degree of stability, without introducing waste by requiring a new application for approval after each small change. This will require co-operation between the Notified Bodies, Competent Authorities and ethical oversight bodies.
- Informed consent for patients should include the nature of the device and its mechanism of action, an account of local and world experience with the procedure, known risks, the uncertainty around their magnitude, and the possibility of unknown risks. The arguments for proceeding and for using an established alternative technique should be explained fairly. To minimise bias in consent, a digital decision support tool or a neutral party such as a research nurse should be employed.

- Notified bodies and other assessors should be enabled and encouraged to provide guidance to innovators about the nature of the clinical studies and outcomes which will be helpful in evaluating market access application via CE marking. These should be consistent with established frameworks for clinical evidence development.
- Low quality evidence such as that from compassionate use cases, or arguments based on equivalence should not be accepted as the sole basis for granting market access, except for Class 1 devices without any novel features. For rarely used or "orphan" devices, licenses with post-market data collection conditions should be used to ensure that key data is recorded and made public in every case of use.

7. Ethical requirements for pivotal evidence development phase

In this phase the aim of evaluation is to establish the relative clinical effectiveness and cost-effectiveness of devices, and to explore their risks in a larger representative population of patients. Randomised trials (RCTs) are the best method for establishing relative effectiveness, but preparatory studies are often required for therapeutic devices, to avoid common sources of bias, confounding and failure to recruit.

- A full disclosure of conflicts of interest is required from all parties involved in development, testing, promotion and marketing of a medical device.
- Unbiased informed consent procedures which clarify the worldwide and local experience and outcomes with the device should be used (see above).
- All practicable measures should be taken to minimise any harm to patients resulting from the learning curves of clinical teams: this includes:
  - Using prior simulation, training and assessment of learning on models, cadavers or live animals to prepare clinical teams.
  - Developing valid measures of procedural quality which can be used to evaluate learning, and using these measures to decide whether clinical teams are ready to enter an RCT.
  - Making arrangements for training and mentoring during the clinical learning curve to minimise risk to patients.
  - Incorporating an independent expert review of adverse events to identify whether clinical learning played a role in them and to make recommendations.
- Health technology assessment for highly innovative or disruptive technologies should include consideration of the costs (including opportunity costs) and risks if the technology is widely adopted across the healthcare system. The risks considered should include de-skilling of clinical teams in using alternatives to the innovation, and the broader costs of modifying clinical practice, treatment pathways and business models.
- Health technology assessment should analyse the environmental impact of widespread adoption of new technology in terms of its net carbon footprint, and its potential impact on equity of access to care for costly innovations.
- Studies should aim to include patients which represent the diversity of the society in which they are conducted, ensuring that data is collected to determine whether inter-group variations in outcomes exist. Where there is a rationale for expecting outcome differences,

pre-specified subgroup analyses of groups of special clinical interest should be conducted within prospective cohort studies and randomised trials.

- Randomised trials should not be conducted before broad clinical consensus has been achieved on the definition of the device, procedure for use and indications, and arrangements for studying quality of delivery and avoiding harm from learning curves are in place.
- Notified bodies should place conditions on certificates for market access to ensure that the aims of the MDR are achieved for high-risk devices. Initial access available could be only in the context of RCTs or other appropriate studies whose results should be reviewed by the Competent Authority before full access is granted or the device is withdrawn.

8. Ethical requirements for the post-market surveillance phase

- Governance, curation and funding of registries should be distributed amongst different entities to avoid conflicts of interest.
- The MDR requirements for post-market surveillance studies for high risk devices should be fulfilled by imposing conditions on market access which require innovators to report key outcome data on all devices for a specified period of time and making the results publicly available.
- Devices whose performance is dependent on Artificial Intelligence should undergo regular re-evaluation to ensure that algorithm changes through machine learning have not resulted in any unexpected performance changes, or unintended increases in device autonomy, or drift in use. Any such enhanced capacities will require reporting and investigation.
- Restrictions on data sharing inhibit research and analysis, and should be avoided unless strong justification is presented. Curators of registries and large repositories of health data should be required to give access to bona fide non-commercial researchers in order to maximise the potential of linkage of big data.
- Patients have a duty to allow the data about treatments they are receiving to be used for the benefit of others where no risk of harm to them is involved. The use of anonymised (or pseudonymised) data in such research should therefore be a standard component of consent for treatment, with patients having an “opt out” if they do not wish to participate.
- Studies using linked datasets should comply with evidence-based guidelines on the correct use of data, appropriate study methodology and thresholds for data quality.

9. Other ethical recommendations

- Editors and publishers of clinical research journals have a responsibility to represent the current state of knowledge about devices accurately. This implies that studies showing positive and negative outcomes should be treated equally, avoiding success bias, and that conflicts of interest are declared clearly and fully.
- Research grant funding panels should prioritise support for studies which offer the largest potential improvements in human health and wellbeing, but balance this by setting aside reserve funding for studies of important rare conditions where evidence about treatment effectiveness is lacking.
- Policy makers have an ethical obligation to act when evidence emerges that current arrangements have specific weaknesses which result in licensing without adequate evidence of performance and safety, inhibit improvements in evaluation methods or add unnecessary costs and delays to the process of evaluation.

10. Commentary

This document sets out in detail the main implications of adopting a particular ethical framework to underpin the work of evaluating and licensing therapeutic medical devices in the EU. The arguments in favour of having an explicit ethical framework for this activity, as summarised in earlier sections of the document, are in our view, compelling. Some specific implications, however, present challenges to current ways of working, which may be inconvenient or costly.

We have explained the reasons for our choices, but it would certainly be possible to propose alternative frameworks. All conceivable alternatives would also throw up challenges to current practices, albeit different ones, and deciding not to have an ethical framework in order to avoid the implications would itself clearly be unethical. So would ignoring the document. We would therefore like to stimulate responses to this proposed charter from national regulators, notified bodies, health technology assessment organisations, patients' associations, medical device manufacturers, EU policy makers in the field of medical devices, and clinical professional bodies at national and European levels. The document could be usefully improved by input from these bodies, but more importantly, by engaging in dialogue about improving it, the bodies listed would be endorsing the need for a framework of this type, and would be helping to create it. Although compliance with the framework would likely remain voluntary, its existence would facilitate challenges to practices which appear to run counter to its recommendations, and thereby improve the capacity of the system as a whole to achieve its functions in terms of ensuring that devices are safe and perform their functions in the expected manner.

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CORE-MD, Coordinating Research and Evidence for Medical Devices, aims to translate expert scientific and clinical evidence on study designs for evaluating high-risk medical devices into advice for EU regulators.

For more information, visit: www.core-md.eu

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