CORE-MD

Coordinating Research and Evidence for Medical Devices

Notes of Advisory Board Meeting

10/11/2021

The meeting started with a Tour de Table from all the participants.

1. Origins and scope of the CORE–MD project

Paul Piscoi as chair of the Advisory Board then opened the discussion with an overview of the Medical Device Regulation (MDR), which is the new EU regulatory framework. He stressed the importance of clinical evidence, investigations and data used to prove the conformity of high-risk clinical devices with the requirements of Annex I of the MDR (concerning "General Safety and Performance Requirements"). The MDR provides a legal basis for European common specifications to be developed and adopted, which would be technology-specific and mandatory, as opposed to international medical device standards (for example from ISO/CEN) which are voluntary. CORE-MD can contribute by developing recommendations that may lead to the development of common specifications.

2. General discussion – project objectives

- **Understanding methods used to generate clinical evidence for high-risk medical devices**
- **Strengthening clinical evidence for high-risk medical devices**
- **Extracting maximal value from medical device registries and real-world evidence**

Discussion around current methods of evidence generation. CORE-MD will focus initially on some specific product groups: cardiovascular (including stents, and devices for valve repair or replacement), orthopaedic (hip and knee replacements), and diabetic (artificial pancreas, insulin pumps). This session focussed on producing guidance.

- The view from **TGA in Australia (SS)** is that clinical evidence guidelines have to be living documents, which need to be constantly updated in view of the state of the art.
- Similar devices may be supported by very different studies. Australia is in a privileged position since most new devices that they see have already been subject to regulatory approvals in the EU and the US. In some of the areas there is a huge disparity in terms of the actual requirements. Unless the EU puts something down concerning trial design or what needs to be reached as an end-point, their interpretation is that there can be considerable variation between Notified Bodies in what they approve, for example with small numbers of subjects which they consider inappropriate. For orthopaedic devices, the vast majority of the devices come to market through claims of equivalence.

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- Concepts of what could be a 'generic device' are a challenge. What the regulators often see, is iterative innovation instead of completely new devices. It is difficult to get definitive guidance.
- **US perspective, FDA (MT)**: Could objective performance criteria be a tool to provide a sustainable approach for evaluating well-established devices? This is established in the US but development will depend on particular products and marketing pathways. The FDA is always considering how best to develop methods for evaluating devices, according to their specific type.
- Industry experience of using patient-reported outcomes? If they receive a specific request then MedTech Europe will consult internally to identify appropriate expertise within their members (DP).
- Experience of statistical methodologies applied, from Notified Bodies (AS): Having very clear criteria for statistically valid outcome variables, published in guidance, would be very helpful. UK ISO committee is drafting a standard for clinical evaluation of medical devices (coordinated by Amie Smirthwaite).
- Recommendation from AS to select good case studies for the systematic reviews, go back to 10-15 years and see how controversial or non-controversial devices were assessed. How were they assessed, and in retrospect how were some "wrong" decisions made? Examine the advantages and disadvantages of different data sources. This could be interesting in the clinical settings that CORE-MD is focussing on.
- ISO 14155 task force did search for regulatory references when the last standard was prepared (DG). Two from the US were the most complete, and there was a short document from UK. Defining standards for a moving target is difficult, to write something which can be valid even in 2 years from now. There is a need constantly to adapt. The US has a system to bridge from written guidance with reviews or pre-submission meetings. This might be something that could help to streamline the process a bit more in Europe also.
- Experience of an EU regulator (WE): As well as drafting some preliminary device-specific guidance which may be a precursor of common specifications, and which would expand on the criteria given in Annex XIV of the MDR, it would be useful if CORE-MD could consider how to establish some kind of infrastructure that could be used to update the clinical evidence and the state-of-the-art. That would also be very important for the registries, so CORE-MD should involve registry organisations as much as possible.
- Really important for CORE MD to promote discussion of pragmatic trials of devices, including the utility of registry-based randomised controlled trials (PJ). With implantable devices, compliance is assured and after randomisation follow-up can be much more straightforward than in drug trials. Also need to correct the misconception that real-world evidence can serve the same need.
- From an ethical perspective, these approaches are good (SOH) but it is important to consider questions of equity to ensure that no-one is exploited. Weak legislation is one country should not

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make it possible to do things which would not be possible otherwise. This certainly arise with countries with weak legislation and very inefficient healthcare.

- View from Swiss regulator (IS): CORE MD is focussing on high-risk devices, and in established fields many patients respond well to devices and treatments that are already available. Some patients who do not, will need innovation, but in the past there has been input that even more innovative devices should reach the market based on not much more than hypothesis, and that real-world data concerning the risk-benefit ratio would then identify sub-populations. That could jeopardise the safety of patients who are well served; there is right of the patients to be informed about experimental devices and not just exposed because these devices easily reach the market. CORE MD could consider how to involve patients more and respect their rights.

Discussion focussing on requirements for real-world evidence and registries (relating to tasks in WP3, introduced by RN)**.** Why were data from registries not used in the past?

- (PP) Access to data and lack of communication between the registries themselves, and with regulators. There are no lines for constant communication. Even more important for the industry.
- (SS) Some registries are used more than others, depending on complexity and completeness of datasets. Orthopaedic societies have more easy and relevant end-points. For pre-market context more difficult.
- There are specific situations where it is better not to use registries and where RCTs are indeed appropriate and feasible. Otherwise, in the absence of a comparator device or state-of-the-art data, it would be necessary to make a very good case. The main limitation is when less stringent evidence is brought forward in a pre-market application that has been contingent on the device getting into registries somewhere else; at the moment TGA does not have mechanism to grant provisional approvals that require continuing follow-up.
- Registries provide the highest quality and most ready to use real-world evidence.
- (NMcA): The new MDR does offer the opportunity to formalise the use of new tools such as device-specific guidance, to legalise requirements for evidence that would be mandatory. Embrace it as a future opportunity, so the contribution of CORE MD can be essential.
- (From Team NB): there is a need to define minimum criteria of acceptability, and to identify statistical control, and the claims that are possible for safety.
- EMA has held workshops on registries and has a number of documents on their website (FS). https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries
- MedTech Europe (DP): registries have not been used extensively because there are no standards for their quality, and because there have been difficulties identifying which devices are covered and accessing their data. Some harmonisation would be extremely useful.

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- (DG): There is a gap between scientific and regulatory needs not only in registries but in pre-market studies, when a protocol is developed only for scientific needs or only for regulatory needs. Both should be taken into account to define good data that can be used both for scientific and regulatory purposes. This is relevant for all types of studies.

Global regulatory convergence (introduced by AF)

Regulatory convergence:

- Regulatory policy should be based on scientific and clinical evidence
- Clinical evidence should be transparent
- Standards for safety and performance should be the same everywhere
- Competition to develop a regulatory environment that is most favourable to early device innovation is inappropriate. Risks should be shared everywhere where people are volunteering to participate in a study. There should not be a competition to make it easier to make early-phase studies in one regulatory environment rather than another
- Clinical research and standards for best practice are global
- Regulatory convergence is logical but how can academic consortia such as CORE-MD contribute?

Artificial intelligence and machine learning in medical devices (introduced by FR)

Discussion around AI and machine learning:

- IMDRF chair in 2022 will be Australia. For the IMDRF working group on AI, CORE MD can contact the chair to express an interest in intervening directly or during the consultation phase.
- COCIR will nominate experts to this CORE MD task with involvement for DITTA also in IMDRF. There is a new work item proposal on the clinical evaluation of AI in ISO (TC62) and IEC.
- COCIR interested particularly in the interaction between manufacturer – device – user and the responsibility and liability that lies with the manufacturer and the user in the post-market phase. What the human oversight constitutes, how the information flows, how we deal with challenges, etc. We need a good alignment between regulators, users and industry.
- COCIR (LH): Regulations are not written for AI. We would need to focus on the implication, the impact and the real life use. The user group is often very different from the group on which the AI algorithm was trained, validated and tested. Therefore, unexpected impact and difficulties might arise.

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General discussion / concluding comments

- From EMA (AHS): There could be considerable overlap and synergies between the CORE-MD task on registries, and the development of registries for pharmaceutical products as considered by EMA, so it would be useful to share experience.
- Collaboration on quality criteria for registries, with MDEpiNET, would be excellent (AS). IMDRF documents and criteria merit reassessment and revision, jointly with regulators.
- Infrastructures for keeping regulatory guidance and systems up-to-date will be needed (WE). For example, a Registry Working Group at Commission level would be useful. All stakeholders need access to good-quality registries providing valid data.
- HPRA strongly supports the CORE-MD initiative (NMcA).
- EMA has a big data task force, with the member competent authorities (FS). Contact with CORE MD would be possible.
- Closer consensus on devices, globally, would be useful (SS). Much closer with medicines currently, but much potential.

The next meeting will be scheduled in mid-2022.

Figure 1. Participants of the Advisory Board meeting

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