CORE-MD

Coordinating Research and Evidence for Medical Devices

Peer-reviewed manuscripts

Deliverable 1.3

Deliverable factsheet

Source Activity:	Work package 1, Task 1.1
Title:	Peer-reviewed manuscripts
Lead Beneficiary:	BUH / Insel Gruppe AG
Nature:	Report
Dissemination level:	Public
Editor:	André Frenk (BUH / Insel Gruppe AG)
Authors:	Arjola Bano (BUH / Insel Gruppe AG), Anne Lübbeke (UOXF), Georgios Siontis (BUH / Insel Gruppe AG), Stephan Windecker (BUH / Insel Gruppe AG)
Status:	Final
Date:	31/03/2024
Contractual Delivery Date:	Month 24

Version Log

Issue Date	Version	Involved	Comments
14/09/2023	1.0	André Frenk (BUH / Insel Gruppe AG), Arjola Bano (BUH / Insel Gruppe AG), Anne Lübbeke (UOXF), Georgios Siontis (BUH / Insel Gruppe AG), Stephan Windecker (BUH / Insel Gruppe AG)	First draft
31/03/2024	2.0	André Frenk (BUH / Insel Gruppe AG)	Second and semi-final version with inclusion of the final diabetes' results and respective references
29/04/2024	2.1	Alan Fraser (ESC), Valentina Tageo (ESC)	Final editing and submission with inclusion of the links to the publications and open datasets

Note for the reviewers: the present deliverable was finalised towards the end of the project in order to add the relevant references and links to the published articles and FAIR open datasets. Similarly to the other research-

intensive tasks that characterized the work conducted in the CORE-MD Coordination and Support Action, the Task 1.1 required a considerably higher effort than expected due to the breadth and complexity of the three systematic reviews and meta-analyses conducted across the three selected medical specialties (cardiology, orthopaedics, and diabetes). These studies have generated highly relevant results that are concisely presented in this deliverable and described in detail in the respective manuscripts which submission and acceptance further delayed the finalization of the deliverable. Nonetheless, the preliminary and intermediate results of the studies were regularly shared with the interested WP and task leaders as well as presented at relevant project meetings, regulatory and scientific fora thus not affecting the progression of the other activities.

Acronyms and abbreviations

AID	Automated Insuline Delivery
BUH	Bern University Hospital
CGM	Continuous Glucose Monitoring
EFORT	European Federation of National Associations of Orthopaedics and Traumatology
ESC	European Society of Cardiology
RCSI	Royal College of Surgeons in Ireland
RCT	Randomized Controlled Trial
UOXF	University of Oxford

Table of Contents

Executive Summary

The task 1.1 within the Work Package 1 focused on the conduction of systematic reviews of the scientific literature to evaluate the type of clinical evidence available for high-risk medical devices approved for clinical use in Europe since 1990. Three medical fields using high-risk (Class III) medical devices have been selected: cardiovascular, orthopedics and diabetics. The evaluation of the devices in the cardiovascular and diabetics fields were performed by the Bern University Hospital (BUH, Insel Gruppe AG). The review of the devices in the orthopedic field by the by the Geneva University Hospitals and University of Oxford.

The overall aim of the task was to map the existing evidence on high-risk medical devices through broad systematic reviews of the medical literature and to evaluate characteristics of the available evidence through meta-epidemiological assessments.

To this end, detailed study protocols were drafted and published online in peer-reviewed journal before initiation of the systematic review and are available for consultation in the Deliverable D1.1.

The focus of the work has been on methodologies and types of investigational clinical studies, study-specific characteristics, underlying study populations, interventions considered as control, comparators, type of outcomes and the applied statistical methods.

The following papers have been published or submitted for publication.

Cardiovascular devices

George C M Siontis, Bernadette Coles, Jonas D Häner, Laurna McGovern, Joanna Bartkowiak, J J Coughlan, Alessandro Spirito, Roberto Galea, Andreas Haeberlin, Fabien Praz, Daijiro Tomii, Tom Melvin, André Frenk, Robert A Byrne, Alan G Fraser, Stephan Windecker, for the CORE-MD Investigators, **Quality and transparency of evidence for implantable cardiovascular medical devices assessed by the CORE-MD consortium**, *European Heart Journal*, 2023;, ehad567, https://doi.org/10.1093/eurheartj/ehad567.

Orthopedic devices

Anne Lübbeke, Christophe Combescure, Christophe Barea, Amanda Inez Gonzalez, Keith Tucker, Per Kjærsgaard-Andersen, Melvin T, Alan G Fraser, Rob Nelissen, James A Smith, **Clinical investigations to evaluate high-risk orthopaedic devices: systematic review of the peer-reviewed medical literature**, EFORT open reviews vol. 8,11 781-791. 1 Nov. 2023, https://doi.org/10.1530/EOR-23-0024.

Diabetic devices

Arjola Bano, Juri Künzler, Faina Wehrli, Lum Kastrati, Tania Rivero, Alan G. Fraser, Christoph Stettler, Roman Hovorka, Markus Laimer and Lia Bally, on behalf of CORE-MD investigators, **Clinical evidence for high-risk CE-marked medical devices for glucose management: a systematic review and meta-analysis**, submitted for publication to *Diabetes, Obesity and Metabolism*.

The datasets of the clinical evidence and of the different methodologies used for the three investigated categories of medical devices have been made freely available to all participants of the consortium and to other researchers to facilitate future projects and analyses via the open Zenodo CORE-MD Community (https://zenodo.org/communities/core-md) see Deliverable D1.2).

Moreover, relevant information related to inclusion of specific subgroups (i.e. sex-specific) across studies in different phases of devices evaluation has been collected and analyzed. The preliminary results of such complementary analyses have been presented at the last Project board meeting in Brussels on March 14th, 2024, and a scientific paper titled "Inclusion of subjects and reporting by age, sex, and ethnicity in clinical trials of high-risk medical devices approved in the European Union" authored by JJ Coughlan (RCSI) et al. is in preparation.

The present deliverable provides a summary of each paper and refer to the published studies for more detailed information.

1 Cardiovascular devices

1.1 Background and aim

The European Union Medical Device Regulation 2017/745 challenges key stakeholders to follow transparent and rigorous approaches to the clinical evaluation of medical devices. The purpose of this study is a systematic evaluation of published clinical evidence underlying selected high-risk cardiovascular medical devices before and after market access in the European Union (CE-marking) between 2000 and 2021.

1.2 Methods

Pre-specified strategies were applied to identify published studies of prospective design evaluating 71 high-risk cardiovascular devices in seven different classes (bioresorbable coronary scaffolds, left atrial appendage occlusion devices, transcatheter aortic valve implantation systems, transcatheter mitral valve repair/replacement systems, surgical aortic and mitral heart valves, leadless pacemakers, subcutaneous implantable cardioverter-defibrillator). The search time span covered 20 years (2000–21). Details of study design, patient population, intervention(s), and primary outcome(s) were summarized and assessed with respect to timing of the corresponding CE-mark approval.

1.3 Results

At least one prospective clinical trial was identified for 70% (50/71) of the pre-specified devices. Overall, 473 reports of 308 prospectively designed studies (enrolling 97 886 individuals) were deemed eligible, including 81% (251/308) prospective non-randomized clinical trials (66 186 individuals) and 19% (57/308) randomized clinical trials (31 700 individuals). Pre-registration of the study protocol was available in 49% (150/308) studies, and 16% (48/308) had a peer-reviewed publicly available protocol. Device-related adverse events were evaluated in 82% (253/308) of studies. An outcome adjudication process was reported in 39% (120/308) of the studies. Sample size was larger for randomized in comparison to non-randomized trials (median of 304 vs. 100 individuals, $P < .001$). No randomized clinical trial published before CE-mark approval for any of the devices was identified. Non-randomized clinical trials were predominantly published after the corresponding CE-mark approval of the device under evaluation (89%, 224/251). Sample sizes were smaller for studies published before (median of 31 individuals) than after (median of 135 individuals) CE-mark approval ($P < .001$). Clinical trials with larger sample sizes (>50 individuals) and those with longer recruitment periods were more likely to be published after CE-mark approval, and were more frequent during the period 2016–21.

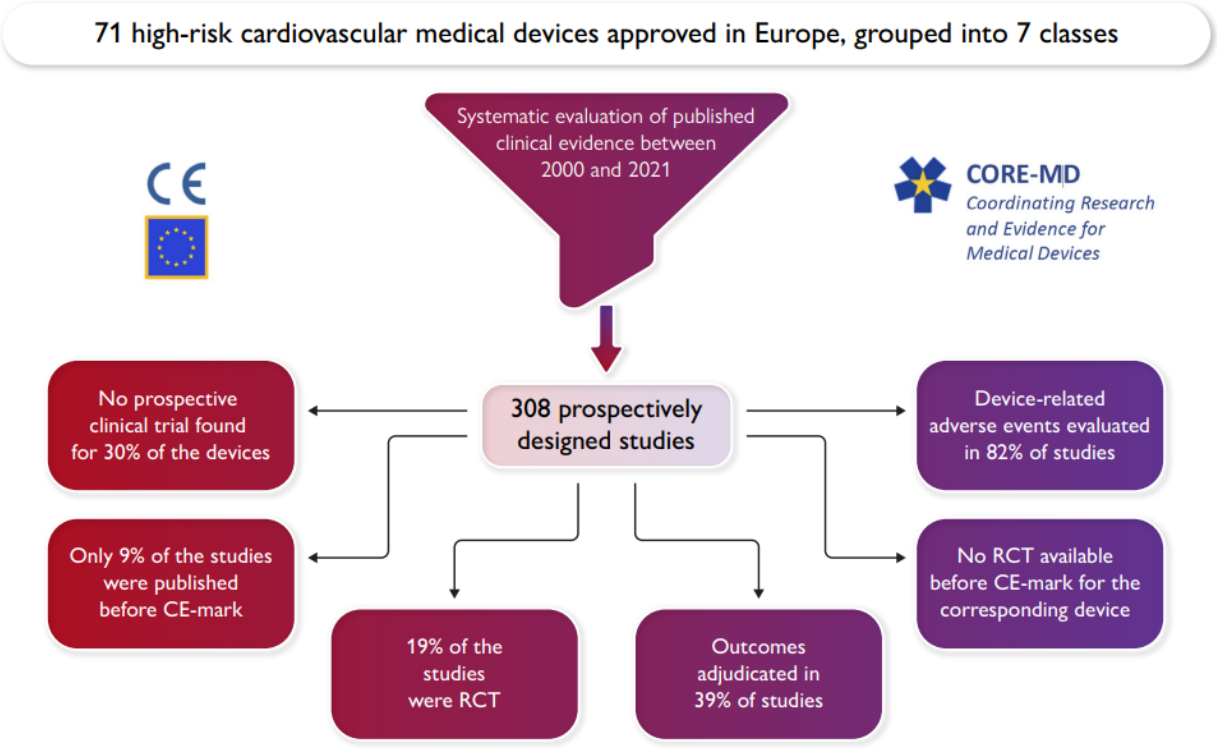

Figure 1. Systematic evaluation of published clinical trials with prospective design for 71 high-risk cardiovascular devices during the period 2000–21 (Siontis *et al.*, Eur. Heart Journal 2023 [1])

1.4 Conclusions

The quantity and quality of publicly available data from prospective clinical investigations across selected categories of cardiovascular devices, before and after CE approval during the period 2000–21, were deemed insufficient. The majority of studies was non-randomized, with increased risk of bias, and performed in small populations without provision of power calculations, and none of the reviewed devices had randomized trial results published prior to CE-mark certification.

2 Orthopedic devices

2.1 Background and aim

The objective of this systematic review was to give an overview of clinical investigations regarding hip and knee arthroplasty implants published in peer-reviewed scientific medical journals before entry into force of the EU Medical Device Regulation in May 2021.

2.2 Methods

We systematically reviewed the medical literature for a random selection of hip and knee implants, to identify all peer-reviewed clinical investigations published within 10years before and up to 20years after regulatory approval. We report study characteristics, methodologies, outcomes, measures to prevent bias, and timing of clinical investigations, of 30 current implants. The review process was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.3 Results

We identified 2912 publications and finally included 151 papers published between 1995 and 2021 (63 on hip stems, 34 on hip cups, 54 on knee systems). We identified no clinical studies published before CE-marking for any selected device, and no studies even up to 20 years after CE-marking in one quarter of devices. There were very few randomized controlled trials, and registry-based studies generally had larger sample sizes and better methodology. All data are publicly available on Open Science Framework (https://osf.io/6gmyx) and in the CORE-MD Zenodo community (https://zenodo.org/communities/core-md, see Deliverable D1.2). The results of the study were first published in pre-print version in the free online specialized archive medRxiv [2] and subsequently accepted for publication by EFORT Open Reviews [3].

2.4 Conclusions

The peer-reviewed literature alone is insufficient as source of clinical investigations of these high-risk devices intended for life-long use. A more systematic, efficient, and faster way to evaluating safety and performance is necessary. Using a phased introduction approach, nesting comparative studies of observational and experimental design in existing registries, increasing use of benefit measures, and accelerating surrogate outcomes research, will help to minimise risks and maximise benefits.

3 Diabetic devices

3.1 Background and aim

High-risk medical devices, in particular automated insulin delivery (AID) systems, represent a paradigm shift in diabetes care. However, there are no specific recommendations in Europe on the design and conduct of studies for high-risk devices. In the framework of the Coordinating Research and Evidence for Medical Devices (CORE-MD) group, we conducted a systematic review and meta-analysis of the evidence for CE-marked high-risk devices for diabetes management.

3.2 Methods

On February 23rd 2022, we searched Embase (Elsevier), Medline All (Ovid), Cochrane Library (Wiley), and Science Citation Index Expanded and Emerging Sources Citation Index (Web of Science), to identify published interventional and observational studies in humans, evaluating the efficacy and/or safety of CE-marked high-risk medical devices for diabetes care, both pre- and post-market. According to the Medical Device Regulation, high-risk medical devices include AID systems, implantable insulin pumps, and continuous glucose monitoring systems (CGM). The selection of studies was performed independently by two researchers. The study protocol was published on PROSPERO [4] and PubMed [5]. We meta-analysed randomized clinical trials (RCTs) that compared the AID systems with other therapies for the treatment of diabetes. Furthermore, we meta-analysed studies that compared the outcomes before and after the utilization of AID systems (i.e., pre-post intervention).

3.3 Results

99 studies published from 2009–2022 were included, comprising 83 on AID systems, 6 on insulin pumps, and 10 on CGM; 43% reported industry funding, and 30% were published before CE-marking. 45% of studies had a comparator group, 33% were RCTs, 25% non-randomized trials, and 41% observational studies. Median sample size was 52 (interquartile range 25–111), age 37.8 years (17–45.5), and study duration 13 weeks (4.5–26). AID systems lowered HbA1c by 0.3% (9 RCTs; I2 85%) and increased time in target range for sensor glucose level by 10.5% (14 studies; I2 89). 69% of studies reported at least one safety or device-related outcome. Bano et al. have submitted the paper describing the results of this study "Clinical evidence for high-risk CE-marked medical devices for glucose management: a systematic review and meta-analysis" for publication to *Diabetes, Obesity and Metabolism*.

3.4 Conclusions

Our systematic review and meta-analysis showed that CE-marked medical devices, in particular AID systems, improved glucose control. However, no studies reported on chronic glucose related complications, and safety outcomes were partially reported across studies. The currently available evidence for CE-marked high-risk medical devices for diabetes care is characterized by small studies with short follow-up time and methodological heterogeneity. This highlights the need for developing standards

for future investigations of high-risk medical devices, thereby improving study comparability and transparency of findings.

4 Summary and conclusions

These systematic evaluations of the published clinical literature for the selected high-risk medical devices in the field of cardiovascular, orthopedic and diabetes care indicate that the clinical evidence available prior to the market release (CE-mark) is generally insufficient. It is characterized by small studies with short follow-up time and methodological heterogeneity. This highlights the need for better guidance documents throughout the different medical fields. The new European Medical Device Regulation should improve the transparency of the clinical evidence used to demonstrate the safety and performance of the medical devices in the pre- and post-market phases.

References

[1] Siontis, G. C. M., Coles, B., Häner, J. D., McGovern, L., Bartkowiak, J., Coughlan, J. J., Spirito, A., Galea, R., Haeberlin, A., Praz, F., Tomii, D., Melvin, T., Frenk, A., Byrne, R. A., Fraser, A. G., Windecker, S., & CORE-MD Investigators (2024). Quality and transparency of evidence for implantable cardiovascular medical devices assessed by the CORE-MD consortium. European heart journal, 45(3), 161–177. https://doi.org/10.1093/eurheartj/ehad567.

[2] Lübbeke, A., Combescure, C., Barea, C., Gonzalez, A. I., Tucker, K., Kjærsgaard-Andersen, P., Melvin, T., Fraser, A. G., Nelissen, R., & Smith, J. A. (2023). Clinical investigations to evaluate high-risk orthopaedic devices: systematic review of the peer-reviewed medical literature. *medRxiv*, https://doi.org/10.1101/2023.08.24.23294479.

[3] Lübbeke, A., Combescure, C., Barea, C., Gonzalez, A. I., Tucker, K., Kjærsgaard-Andersen, P., Melvin, T., Fraser, A. G., Nelissen, R., & Smith, J. A. (2023). Clinical investigations to evaluate high-risk orthopaedic devices: a systematic review of the peer-reviewed medical literature. EFORT open reviews, 8(11), 781–791. https://doi.org/10.1530/EOR-23-0024.

[4] Bano, A., Laimer, M., Wehrli, F., Künzler, J., Stettler, C., Hovorka, R., & Bally, L. (2022). Clinical evidence of high-risk medical devices for diabetes management: A systematic review and meta-analysis. PROSPERO International prospective register of systematic reviews, CRD42022366871. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022366871.

[5] Bano, A., Laimer, M., Wehrli, F., Kunzler, J., Rivero, T., Fraser, A. G., Stettler, C., Hovorka, R., & Bally, L. (2023). Clinical evidence for high-risk medical devices used to manage diabetes: protocol for a systematic review and meta-analysis. BMJ open, 13(4), e070672. https://doi.org/10.1136/bmjopen-2022-070672.

CORE-MD

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

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 965246.