Safety and performance of high-risk medical devices: the role of real-world data

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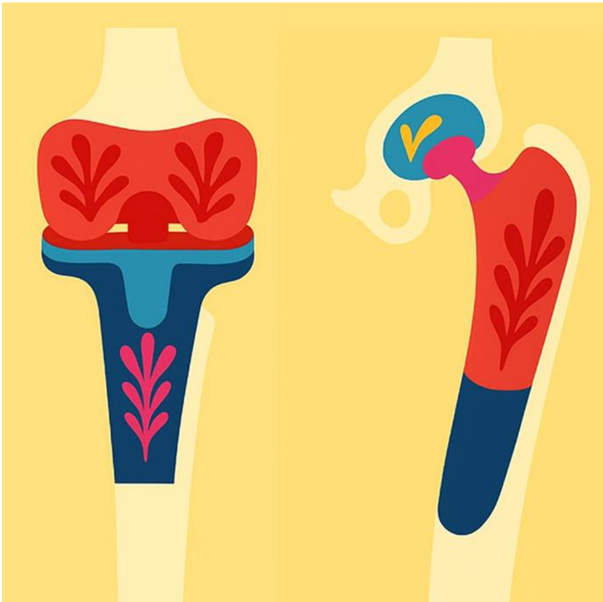
Chapter 4 – Safety notices and registry outlier data measure different aspects of safety and performance of total knee implants: a comparative study of safety notices and register outliers



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Acta Orthop. 2024 Nov 25:95:667-676

Abstract

Background: Safety notices for medical devices such as total knee (TK) implants may indicate problems in their design or performance that require corrective action to prevent patient harm. Safety notices are often published on national Ministries of Health or regulatory agencies websites. It is unknown whether problems triggering safety notices identify the same implants as those identified by registries as "outlier." We aimed to assess the extent to which safety notices and outlier identification in registries signal the same or different TK implants.

Methods: The CORE-MD tool, an automated web scraper tool, was used to collect safety notices related to TK implants on 13 national Ministries of Health websites and regulatory agencies. Safety notices were defined according to the Medical Device Regulation (MDR) as "a communication sent by a manufacturer to users or customers in relation to a field safety corrective action." Identified TK outliers, defined as having a significantly higher revision risk than other comparable TK implants, were extracted from registry reports.

Results: 787 safety notices for 38 TK implants and 35 TK outliers were identified, together identifying 47 unique TK implants. 26 (55%) TK implants had safety notices and were also outliers, 12 (26%) TK implants had only safety notices, and 9 (19%) were outliers only. TK implants with safety notices only had similar types of problems to TK outliers with safety notices, with "Manufacturing/Packaging/Shipping" problems being most frequent (44%). Cumulative revision risks (1/5/10-years) were lower for TK implants with safety notices only than for TK outliers with safety notices.

Conclusion: 55% of the TK with a safety notice were identified as outliers in the registry, whereas around 25% of TK outliers are not the subject of publicly released safety notices, with safety notices pointing to TK implants not identified by registries as potentially

having a higher risk of failure. This suggests that safety notices and registry outlier data measure different aspects of safety and performance.

Background

Medical devices are subject to post-market surveillance (PMS) where manufacturers have to collect and review data on experience with their devices.[1] Once collected, these data must be analysed by the manufacturer to evaluate if any corrective or preventive actions are needed. If action is required to prevent patient harm, a safety notice must be issued.[2] Safety notices can be published on the websites of manufacturers, Ministries of Health, and regulatory agencies. Safety notices may include a recall, amended instructions for use, adverse events, or additional information concerning the device. From a safety and performance perspective, total knee (TK) implants are of interest, as together with total hip implants they are the most used arthroplasty implants.

Safety notices are relevant for clinicians and hospitals as they may guide implant selection. Safety notices can be issued for a wide variety of implant-related issues (e.g. packaging and labelling), which are not always associated with the safety or performance of a TK implant. On the other hand, several arthroplasty registries have procedures in place to identify TK implants with outlier performance (i.e. a significantly higher revision risk than other comparable implants)[3], defined solely based on revision risk.[4,5] Safety notices, however, may also refer to signals based on other outcomes (e.g. poor patient satisfaction scores), meaning that safety notices and outlier identification may reflect different aspects of patient safety. Furthermore, safety notices may be issued based on other data sources such as peer-reviewed publications. Hence, it is unknown whether problems triggering safety notices identify the same TK implants as those identified by registries as outliers.

We aimed to assess the extent to which safety notices and outliers identified by registries signal the same or different TK implants, and to explore possible reasons for any discrepancies.

Methods

Study design

This study focused on the agreement between two real-world data sources that are intended to signal problems related to medical devices, and more specifically to assess whether TK implants for which safety notices were published on the websites of Ministries of Health and regulatory agencies were the same as the TK implants identified and publicly reported by registries as outliers. Only TK implants currently used on the market were included. The study was conducted according the to the STARD guidelines.[6]

Data collection of safety notices reporting TK implants

The Coordinating Research and Evidence for Medical Devices (CORE-MD) PMS tool[7], an automated web scraper tool, was used to identify TK implants with safety notices on the websites of Ministries of Health and regulatory agencies. 13 countries were included in the CORE-MD tool and were therefore assessed in the current study: Australia, Czechia, Denmark, France, Germany, Greece, Ireland, Italy, Portugal, Spain, Sweden, the United States of America (USA), and the Netherlands. Note that all historical and publicly available safety notices were retrieved for each country with their respective last update (Supplementary Table 1 – online available).

Details of the applied methodology in the CORE-MD PMS tool have been published.[7] Briefly, the tool screens the website of each Ministry of Health and regulatory agency to collect all safety information, including safety notices, alerts, and recalls. We refer to safety notices to indicate the collective safety information found on these websites.

To include only safety notices for TK implants currently on the market, a list of all TK implants from the latest annual reports from the following national and regional registries was constructed: American Joint Replacement Registry (AJRR)[8], Australian Orthopaedic Association National Joint Replacement Registry

(AOANJRR)[9], Dutch Arthroplasty Register (LROI)[10], Emilia-Romagna Register (RIPO)[11], German Arthroplasty Registry (EPRD)[12], Swiss National Hip & Knee Joint Registry (SIRIS)[13], and the National Joint Registry for England, Wales, Northern Ireland, the Isle of Man and Guernsey (NJR)[14], and up-to-date registry website data from the Finnish Arthroplasty Register (FAR)[15]. Note that some countries included in the CORE-MD PMS tool to identify safety notices are not used to construct the list of TK implants currently on the market as they lack a(n) (active) regional or national arthroplasty registry capturing data on TK implants[3]. We assumed that safety notices would identify problems that relate to the implant itself rather than reflecting, e.g. limited experience by surgeons or patient case-mix, and thereby that the problems highlighted in these countries would reflect problems elsewhere.

The brand name of each TK implant on this list was used as input for the CORE-MD PMS tool, to extract all associated safety notices for further analysis. Based on the extended safety notice text, the described adverse event was linked to an International Medical Device Regulators Forum (IMDRF) medical device problem code.[16] These IMDRF codes have a hierarchical alphanumerical coding structure, including a letter (i.e. referring to the Annex A in our case) followed by numerical codes at different levels of detail.[16,17] Level one terms are represented by the first two digits, referring to 27 different medical device problems (Table 1). Level two and three terms are described by the digits three to four and five to six respectively, representing a more detailed description of the problem under one of the overarching 27 groups. In this study only the Level one terms were used, as they are already detailed enough to distinguish different device problems. All safety notices related to TK implants were independently classified to an IMDRF code by two researchers (LH and YR); possible discrepancies in coding were resolved by discussion. To determine interobserver variability, the Cohen's kappa (κ) was calculated. Kappa values were categorised into six levels: i) $\kappa \leq 0$ (no agreement); ii) $\kappa = 0.01–0.20$ (none to slight); iii) κ=0.21–0.40 (fair); iv) κ=0.41–0.60 (moderate); v) κ=0.61–0.80 (substantial), and vi) κ=0.81–1.00 (almost perfect).[18] Analysis was performed using Python (version 3.11.5; https://www.python.org/downloads/release/python-3115/).

Data collection of registries reporting TK outliers

Outlier TK implants currently on the market were identified by European registries publicly reporting on TK outliers, as found in a recent systematic review[3] and non-European registries as listed on the website of the AOANJRR.[19] All available registries' annual reports and websites were screened, and any reported TK outlier was extracted. For all extracted TK outliers, it was assessed whether they were reported in the latest annual reports and up-to-date website, representing TK implants currently on the market in these registries. If the TK outlier was not reported in the latest available registry data (i.e. not implanted in the past year in the included registries), the outlier was considered an off-market implant and excluded from further analysis.

TK outlier definitions differed between these registries (AOANJRR: "The revision rate (per 100 component years) exceeds twice that for the group and the Poisson probability of observing that number of revisions, given the rate of the group is significant (*p-value*<0.05)"; NJR: "having a more than twice the prosthesis time incident rate when compared to the group, allowing for confidence intervals"; SIRIS: "Revision rates of more than twice compared to the relevant group"; and the definition of an outlier was not reported for the SAR).[20]

For all TK outliers, the year of first identification and its cumulative revision risks (1/5/10-years), including standard errors (SE) and/or 95% confidence intervals (CI), were extracted. If only the 95% CI was provided, the SE was calculated by subtracting the upper and lower bound of the 95% CI and dividing it by 3.92.[21]

Statistics

First, the overlap between TK implants with safety notices and TK outliers was determined by comparing the brand name reported in both safety notices and registry data. Three groups were distinguished: i) TK implants with safety notices but not identified as an outlier ("safety notices only"); ii) TK implants with both safety notices and identified as an outlier ("both"); iii) TK implants without safety notices but identified as an outlier ("outlier only"). The percentage of TK implants in each of these groups was related to the number of unique TK implants identified by both data sources.

Second, to prevent camouflage (i.e. multiple compatible construct combinations existing within one implant brand name[22]), the overlap between TK implants with safety notices and TK outliers across different variants/subtypes under the same brand name was analysed. We considered possible subtypes with the same brand name by: i) fixation (e.g. cemented *versus* uncemented); ii) stability (e.g. cruciate retaining *versus* hinged), and iii) mobility (e.g. fixed *versus* mobile).

Third, to explore possible reasons for not signalling the same TK implants we examined: i) differences in the frequency of IMDRF codes (Table 1) between the "safety notices only" and "both" groups, and ii) whether the "safety notices only" group had lower cumulative revision risks (and thus seemingly better performance) than the "both" group, which may explain why they were not detected as TK outliers. Random effects models were used to calculate the pooled cumulative revision risks (1/5/10-years) across all registries reporting on the specific TK implant, for the "safety notices only" and "both" groups.

The metafor package in R-statistics (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) was used for analyses.

Ethics, registration, data sharing, use of AI, funding, and disclosures
According to Dutch law, no institutional approval was required. This work was supported by the European Union's Horizon 2020 Research and Innovation 41 Programme (grant number 965246) and was part of the CORE-MD project. Complete disclosure of interest forms according to ICMJE are available on the article page, doi: 10.2340/17453674.2024.42361

Results

TK implants with safety notices

The CORE-MD PMS tool retrieved 104,638 safety notices from 13 Ministries of Health and regulatory agencies websites, of which 1,327 safety notices were considered relevant as they matched with a specific TK implant included in the latest annual registry reports. For the selected 1,327 safety notices, 540 safety notices were excluded because they were not related to a TK implant (i.e. associated with surgical protocols) thus resulting in 787 safety notices included for further analysis (Figure and Supplementary Table 1 – online available). These 787 safety notices were relevant to 38 unique TK implant brand names. Most safety notices originated from the USA and were associated with the Nexgen (Zimmer Biomet) (n=243, 31%) (Table 2).

Outlier TK implants

Four national registries (AOANJRR, NJR, Swedish Arthroplasty Register [SAR], and SIRIS) publicly reported TK outliers while others might report them on a secure website.[3] After removing duplicate TK outlier brand names (i.e. the same brand name was mentioned in multiple annual reports) and off-market TK outliers, 35 unique TK outlier brand names were included for further analysis (Table 3). Supplementary Table 2 (online available) gives more detailed information on specific subtypes within a brand that were identified as outlier along with their performance.

Overlap between TK outliers and TK implants with safety notices

Combining the brand names of the 38 TK implants with a safety notice and the 35 TK outliers resulted in 47 unique TK implant brand names, of which 26 (55%) were in the "both" group, 12 (26%) in the "safety notices only" group, and 9 (19%) in the "outlier only" group (Tables 3 and 4). Thus, safety notices did not signal 9 (26%) of the 35 TK outliers and registries did not signal 12 (32%) of the 38 TK implants that had safety notices.

Considering the 26 TK implants in the "both" group, 7 (27%) TK implants did not have any information in the safety notice regarding fixation, 10 (38%) had no information regarding stability, and 15 (57%) no information regarding mobility, which would be needed to determine whether the exact same TK implant was concerned (white colour, Table 4). Focusing on fixation, 4 out of 26 (15%) TK implants could be matched to the cemented subtype and 6 (23%) to the uncemented subtype (Table 4). With regard to stability, 2 out of 26 (8%) related to the cruciate retaining, 2 (8%) to the hinged, and 8 (31%) to the posterior stabilised subtype. For mobility, one (4%) signalled the fixed, one (4%) the mobile, and five (19%) the rotating subtype. However, 14 (54%) cemented and 3 (12%) uncemented TK implants did not relate to the same fixation subtype (Table 4). Similarly, six (23%) cruciate retaining, two (8%) hinged, and seven (27%) posterior stabilised TK implants did not have the same stability and three (12%) fixed, five (19%) mobile, and two (8%) rotating TK implants did not relate to the same mobility subtype.

Revision rates, timing of safety concerns, and implant problems

For the "both" group, the median 1/5/10-year cumulative revision risks were 1.6% (range: 0.9–9.5), 6.3 (range: 3.6–23.8), and 8.2% (range: 5.6–23.8), respectively, compared with 0.6% (range: 0.3–1.1), 2.3% (range: 1.4–3.7), and 3.8% (range: 3.1–5.1), for the "safety notices only" group (Table 5).

When comparing the dates of the first issuance of safety notices with the dates when the implant was first identified as outlier by registries, no specific data source consistently published safety signals earlier (Table 5).

For the 26 TK implants in the “both” group, 728 safety notices were issued with the most frequently reported problem being related to “A02–Manufacturing, Packaging or Shipping” (43%), followed by “A23–Use of Device” (16%) (Table 6). The most frequent type of problem found was similar for the 12 TK implants in the “safety notices only” group (n=59 safety notices): “A02–Manufacturing, Packaging or Shipping” (44%) (Table 6). Focusing on differences between the two groups, safety notices related to “A05–Mechanical Problem” (6%) and “A17–Compatibility Problem” (8%), respectively, were reported only for the “both” group (Table 6) but not encountered for the “safety notices only” group (Table 6). The interobserver agreement to classify safety notices according to the IMDRF codes among the two observers was substantial (κ=0.79; CI 0.76–0.82).

Discussion

Our study is the first to assess the extent of overlap in TK implants for which safety notices were issued and that were identified as outliers in registry data. We aimed to assess the extent to which safety notices and outlier identification in registries signal the same or different TK implants. We found that approximately half (55%) of the TK implants were identified by both safety notices and registries outlier identification procedures, but a quarter of the TK outliers did not have any publicly released safety notices on the websites of Ministries of Health or regulatory agencies. In addition, there were implant problems identified by safety notices that did not manifest in an outlier status. TK implants with both safety notices and an outlier status had higher cumulative revision risks (1/5/10-years) than TK implants with safety notices only.

A recent review that assessed the current state of medical device safety signal detection stated that a global dataset of medical devices should be created using automatic reports from national/regional databases.[23] In the absence of such a global dataset, the CORE-MD PMS tool was developed recently.[7] Our results add that such a global dataset of safety notices may still not identify a quarter of TK implants with statistically significant poor performance (i.e. TK outliers). Additionally, a published safety notice by itself does not constitute a sufficient and necessary condition for being identified as a TK outlier (the "safety notices only" group). We identified that certain IMDRF codes "A05–Mechanical Problem" and "A17–Compatibility Problem" were not encountered in the "safety notices only" group, suggesting that these are more closely related to poorer implant performance. This observation could result in a helpful indication to highlight a higher risk for certain TK implants with such IMRDF codes identified in safety notices to become an outlier, thus warranting closer scrutiny of these TK implants.

This multi-registry analysis examined the content of safety notice text, which does not typically include information needed to identify specific variants/subtypes of TK implants, characterised by fixation, stability, and mobility. Such a lack of information causes camouflage (i.e. multiple implant subtypes exist under the same implant brand name)[22] making it difficult or even impossible to link the correct TK implants with safety notices to registry data, or to combine data from different real-world data sources. This information is, however, important for action to be taken, as illustrated by a recent study showing good performance for the Nexgen system but significantly higher revision risks for specific combinations with the Nexgen LPS Flex (Supplementary Table 2 – online available).[24] In addition, registries often publicly report only TK implants' brand names without listing more detailed information (e.g. fixation, stabilization, and mobility) to identify which specific subtype of an implant is concerned. Product codes and unique device identifiers (UDIs), which would be needed to deal with such camouflage, were also not reported in safety notices or publicly by registries, except for the American medical device recall database. Accordingly, we highly recommend minimal reporting requirements for manufacturers with respect to safety notices and also for registries when reporting outliers, including: full brand name, fixation, mobility, stability, and product codes or UDIs.

Arthroplasty registries currently only identify TK outliers based on revision risks, which may take several years (at least 1) before sufficient numbers are available to detect performance problems.[3,4] Using revision risk may seem a relatively straightforward endpoint (the occurrence of revision surgery), but surgeon, implant, and patient factors determine whether an implant is revised. Moreover, between-registry variation exists regarding definitions and reasons for revision[3,25] although all included registries identifying TK outliers defined revision as “the replacement/removal/addition of one or more prosthetic components”. But, for instance, revisions due to infection are excluded from the all-cause revision risk in the Swedish registry.[26,27] In contrast, the NJR also includes revision due to infection if no prosthetic component was exchanged, which can result in specific TK implants being identified as an outlier in the NJR but not in other registries. Interestingly, the number of TK outliers publicly reported by the AOANJRR is much higher when compared with other registries publicly reporting on outliers. Part of the explanation may be related to the definition, such as the minimum number of implants required for the publication and analysis of implant-specific revision rates, which is much lower in the AOANJRR (500 procedures compared with 2,500 procedures required in the NJR). These heterogeneities highlight the importance of an international agreement on definitions and outcomes, as well as time-points and methodology used for measuring outcomes within registries.

Some safety notices may be released based on implant related problems causing clinical performance issues relating to a specific TK implant but also on a case-by-case analysis (i.e. no minimum number of implants at risk is required), meaning that safety notices may provide an earlier signal of a possible performance problem than registries.[28] Accordingly, registries could use this as a signal to analyse specific TK implants with released safety notices to detect potential adverse trends in performance earlier. However, when considering the timing of safety notices and outlier data being published, none of the data sources consistently released safety signals earlier than any other, highlighting the importance of a multifaced approach combining these two data sources. While this provides relevant information and includes all TK implants for which safety concerns were reported in safety notices or reported as an outlier, it does not answer the question as to what percentage of TK implants did not have any safety concerns reported. It would seem rather infeasible to estimate this percentage based on all TK implants currently on the market in all countries examined in the present study. Creating a random sample of TK implants would be a more feasible alternative to provide such information as a next step.

Limitations

First, the CORE-MD PMS tool searched for safety notices published on the websites of Ministries of Health and regulatory agencies, but we may have missed safety notices if these were reported only on manufacturers' websites, which would have underestimated the number of TK outliers with safety notices. Second, both TK outliers and TK implants not identified as a TK outlier had a relatively similar distribution of IMDRF-problem types, suggesting that the IMDRF code may not be sufficient to distinguish between these two groups. However, only the Level one IMDRF codes were used due to the large number of safety notices to be manually classified, so there may be differences in distribution when Level two or three problem terms were used. On the other hand, one could argue that such differences in these more detailed problem-type descriptions would not likely entail clinically relevant differences in problems. Third, other factors such as surgeon or hospital performance are known to influence revisions, which may skew the revision risks data. Nonetheless, as we used data from four national registries consisting of a large number of TK outliers, the impact on our results is likely to have been small. Fourth, safety notices were collected from websites in more countries than those for which registry outlier identification data were available, which might have underestimated the number of TK outliers and explain part of the “safety notices only” group. On the other hand, assuming that safety notices point to a problem with the implant itself, we would expect any performance issue to be similar across countries and thereby picked up by other registries as well. Finally, our analysis does not exclude possible duplicates of the same safety notices published in different countries or for different models/lots within the country. This is because different countries use diverse formats and criteria to issue safety notices: some countries issue separate safety notices for each model (e.g. the USA, resulting in a high number of safety notices from the USA), while others publish only one safety notice with multiple models. However, the safety notices would still signal the same TK implant, which was used as the unit of analysis in the present study, so excluding duplicate safety notices would not have changed our results.

Conclusion

We found that approximately half (55%) of the TK implants were identified by both safety notices and registries outlier identification procedures, whereas around 25% of TK outliers are not the subject of publicly released safety notices, highlighting the potential of adopting a multifaceted approach, integrating various real-world data sources and methods to combine information to enhance medical device safety signal detection.

Figures and Tables

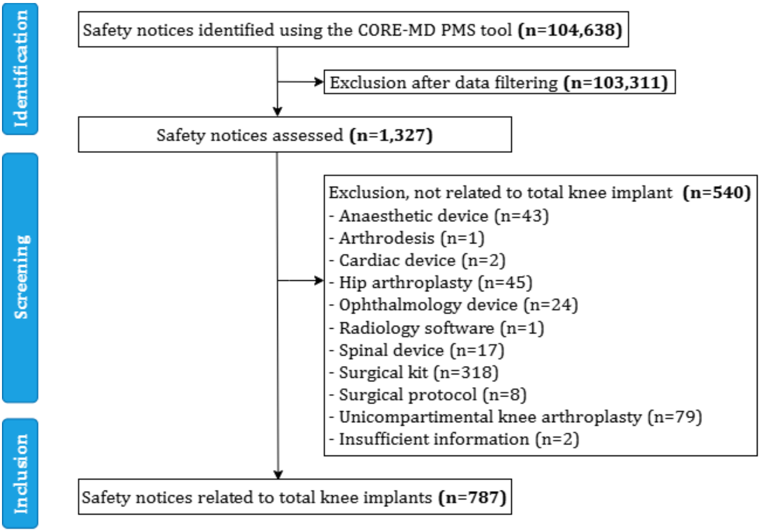

Figure 1. *Flowchart showing the selection process of TK implants with safety notices*

IMDRF code	IMDRF description of medical device problem
A01 – Patient Device Interaction Problem	Problem related to the interaction between the patient and the device.
A02 – Manufacturing, Packaging or Shipping Problem	Problem associated with any deviations from the documented specifications of the device that relate to nonconformity during manufacture to the design of an item or to specified manufacturing, packaging, or shipping processes (out of box problem).
A03 – Chemical Problem	Problem associated with any deviations from the documented specifications of the device that relate to any chemical characterization, i.e. element, compound, or mixture.
A04 – Material Integrity Problem	Problem associated with any deviations from the documented specifications of the device that relate to the limited durability of all material used to construct device.
A05 – Mechanical Problem	Problems associated with mechanical actions or defects, including moving parts or subassemblies, etc.
A06 – Optical Problem	Problem associated with transmission of visible light affecting the quality of the image transmitted or otherwise affecting the intended application of the visible light path.
A07 – Electrical /Electronic Property Problem	Problem associated with the function of the electrical circuitry of the device.
A08 – Calibration Problem	Problem associated with the operation of the device, related to its accuracy, and associated with the calibration of the device.
A09 – Output Problem	Problem associated with any deviation from the documented specifications of the device that relate to the end result, data, or test results provided by the device.
A10 – Temperature Problem	Problem associated with the device producing unintended temperatures.
A11 – Computer Software Problem	Problem associated with written programs, codes, and/or software system that affects device performance or communication with another device.
A12 – Connection Problem	Problem associated with linking of the device and/or the functional units set up to provide means for a transfer of liquid, gas, electricity, or data.

A13 – Communication or Transmission Problem	Problem associated with the device sending or receiving signals or data. This includes transmission among internal components of the device to which the device is intended to communicate.
A14 – Infusion or Flow Problem	Problem associated with the device failing to deliver or draw liquids or gases as intended (e.g. delivering drugs at incorrect rate, problems with drawing fluid from a system). This includes vacuum collection devices and manual or mechanical pumps.
A15 – Activation, Positioning or Separation Problem	Problem associated with any deviations from the documented specifications of the device that relate to the sequence of events for activation, positioning or separation of device. Note: Deployment is synonymous with activation.
A16 – Protective Measures Problem	Problem associated with any deviations from the documented specifications of the device that relate to the implemented and inherited design features specific to devices used for reducing risks to patient or caregiver or maintaining risks within specified levels.
A17 – Compatibility Problem	Problem associated with compatibility between device, patients, or substances (medication, body fluid, etc.).
A18 – Contamination /Decontamination Problem	Problem associated with the presence of any unexpected foreign substance found in the device, on its surface or in the package materials, which may affect performance or intended use of the device, or problem that compromise effective decontamination of the device.
A19 – Environmental Compatibility Problem	Problem associated with the surrounding conditions in which the device is being used such as temperature, noise, lighting, ventilation, or other external factors such as power supply.
A20 – Installation-Related Problem	Problem associated with unsatisfactory installation, configuration, and/or setup of a specific device.

A21 – Labelling, Instructions for Use or Training Problem	Problem associated with device markings/labelling, instructions for use, training and maintenance documentation or guidelines.
A22 – Human–Device Interface Problem	Problem associated with an act or omission of an act that has a different result than that intended by the manufacturer or expected by the operator.
A23 – Use of Device Problem	Problem associated with failure to process, service, or operate the device according to the manufacturer's recommendations or recognised best practices.
A24 – Adverse Event Without Identified Device or Use Problem	An adverse event (e.g. patient harm) appears to have occurred, but there does not appear to have been a problem with the device or the way it was used.
A25 – No Apparent Adverse Event	A report has been received but the description provided does not appear to relate to an adverse event. This code allows a report to be recorded for administration purposes, even if it does not meet the requirements for adverse event reporting.
A26 – Insufficient Information	An adverse event appears to have occurred but there is not yet enough information available to classify the device problem.
A27 – Appropriate Term/Code Not Available	The device problem is not adequately described by any other term. Note: this code must not be used unless there is no other feasible code. The preferred term should be documented when submitting an adverse event report. This information will be used to determine if a new term should be added to the code table.

Table 1. *The 27 International Medical Device Regulators Forum (IMDRF) medical device problem codes and relevant description*[15]

Implant	Au	Cz	Dk	Fr	Ge	Gr	Ir	It	Ne	Sp	Sw	USA
Active Knee	1											
Advance				1				1				11
AGC Anatomic	2	1		1				1				2
Attune			1	1	3		2	2	1			20
Balansys	1	1		1	3			2				
Columbus	1				1							
Duracon	1		1					1				3
EFK					1							
Endo-Model			1	1	4		1	2		2	1	4
Evolution					2			1				3
Gemini							1			1		
Genesis	2	1		1	11	1		3	1	2		16
GMK					1		2	3				3
Innex		1			7		1	2	1	1		
iTotal					1							8
Journey	3		1	1	2			1	1	1		4
Kinemax												1
K-mod									1			
LCS					4		2	3				32
Legion					6			1	1			23
METS Smiles												1
MRK									1			
Multigen		1		1				1		1		
Mutars	1				1							
Natural-knee												1
Nexgen	2		5	1	14		8	5	1		1	206
Noiles			1		1		2	1				6
Optetrak	2					1			1			47
Persona	2		1		5			8				24
PFC Sigma					5		2	2				21
Physica								2				
Saiph	1											
Score	1				1							
Scorpio		1			4		4	2	1			23
TC-plus					1							
Triathlon	6				5		2	6		1		32
Unity					1							4
Vanguard	3	1			3	1		1	3			45

Table 2. *TK implants with the number of safety notices by country*

Outlier TK implant	Outlier reported	TK implants implanted	Identified by the CORE-MD PMS tool (number of safety notices)
ACS	AOANJRR, NJR	2,900	No
Active Knee	AOANJRR	7,215	Yes (1)
Advance	AOANJRR	1,009	Yes (12)
AGC Anatomic	SAR		Yes (7)
Apex Knee	AOANJRR	513	No
Attune	AOANJRR	854	Yes (30)
Columbus	AOANJRR	6,334	Yes (2)
Duracon	SAR		Yes (6)
E.Motion	AOANJRR, NJR, SIRIS	AOANJRR: 1,014; NJR: 339	No
Endo-Model	NJR	309	Yes (16)
Gemini	AOANJRR	21	Yes (2)
Genesis	AOANJRR, NJR, SAR	AOANJRR: 826; NJR 9,190	Yes (38)
Journey	AOANJRR, NJR, SAR, SIRIS	AOANJRR: 3,033; NJR 1,714	Yes (14)
Kinemax	SAR		Yes (1)
LCS	AOANJRR, NJR	5,729	Yes (41)
Legion	AOANJRR, SAR	AOANJRR: 1,017	Yes (31)
Maxim	AOANJRR	413	No
METS Smiles	NJR	954	Yes (1)
Miller-Galante	SAR		No
Mutars	AOANJRR	357	Yes (2)
Nexgen	AOANJRR, SAR	AOANJRR: 316	Yes (30)
Noiles	NJR	594	Yes (11)
Optetrak	AOANJRR, NJR	4,098	Yes (51)
Persona	SAR		Yes (40)
PFC Sigma	AOANJRR, SAR	AOANJRR: 316	Yes (30)
Physica	SIRIS		Yes (2)
Profix	AOANJRR, SAR	AOANJRR: 1,895	No
Rotaglide Plus	AOANJRR	631	No
Score	AOANJRR	4,686	Yes (2)
Scorpio	AOANJRR	1,172	Yes (35)
TC-plus	AOANJRR	63	Yes (1)
Trekking	AOANJRR	1,263	No
Triathlon	SAR		Yes (52)
Vanguard	AOANJRR, SAR	AOANJRR: 6,225	Yes (57)

TK = total knee; CORE-MD = Coordinating Research and Evidence for Medical Devices; PMS = post-market surveillance; AOANJRR = Australian Orthopaedic Association National Joint Replacement Registry, SIRIS = Swiss National Hip & Knee Joint Registry, SAR = Swedish Arthroplasty Register, NJR = National Joint Registry for England, Wales, Northern Ireland, the Isle of Man and Guernsey.

Table 3. *Outlier TK implants currently used on the market*

Implant name	Fixation Cemented		Stability			Mobility		
	Yes	No	Cruciate retaining	Hinged	Posterior Stabilised	Fixed	Mobile	Rotating
Active Knee	No	Yes						
Advance								
AGC Anatomic	No				No	No		
Attune	Yes	Yes	No		Yes	No		Yes
Columbus		Yes						
Duracon	No				No			
Endo-Model	No	No		Yes	No		No	Yes
Gemini								Yes
Genesis	Yes	Yes	Yes		Yes		No	
Journey	No							
Kinemax	No				No			No
LCS	No				Yes	No	No	Yes
Legion	No		Yes	No	Yes			
METS Smiles								
Mutars								
Nexgen	No	Yes	No	No	Yes	Yes	No	Yes
Noiles	No			Yes				No
Optetrak	Yes				Yes			
Persona	No	No	No		No			
PFC Sigma	Yes	Yes			Yes			
Physica					No			
Score	No	No					No	
Scorpio	No		No		Yes			
TC-plus								
Triathlon	No		No		No			
Vanguard								

' ' = total knee implants without any information reported in the safety notice on specific fixation/stability/mobility methods. Yes = total knee implants with information in the safety notice about its fixation, stability, or mobility, thus overlapping with an outlier implant based on its implant characteristic (fixation/stability/mobility). No = total knee implants with information in the safety notice about its fixation, stability, or mobility method but without overlapping with an outlier implant based on its implant characteristics (fixation/stability/mobility).

Table 4. *Overlap of total knee implants in the "both" group based on fixation, mobility, and stability*

Implant	Date of first safety notice	Identified as outlier	Year first identified as outlier and registry reporting	Pooled cumulative revision risk (CI) for specified implant brand name		
				1-year	5-year	10-year
Active Knee	21/10/2016	Yes	2016 (AOANJRR)	1.1 (0.9–1.4)*	5.0 (4.6–5.6)*	8.8 (8.1–9.5)*
Advance	11/07/2016	Yes	2013 (AOANJRR)	2.0 (1.3-3.1)*	6.4 (5.0-8.2)*	8.1 (6.4-10.2)*
AGC Anatomic	21/07/2015	Yes	2014 (SAR)			
Attune	29/06/2015	Yes	2023 (AOANJRR)	1.8 (1.0-3.0)*		
Balansys	29/01/2014	No		0.9 (0.5-1.2)*§¥‖	3.1 (2.3-3.9)*ǂ§¥‖	5.1 (2.2-8.1)*§
Columbus	17/01/2008	Yes	2009 (AOANJRR)	1.2 (0.9-1.5)*	4.4 (3.7-5.3)*	7.3 (6.0-8.8)*
Duracon	20/09/2007	Yes	2004 (SAR)			
EFK	15/04/2014	No		0.6 (0.1-1.2)‖	1.7 (0.5-3.0)‖	
Endo-Model	16/04/2012	Yes	2019 (NJR)	1.3 (0.8-2.2)†	4.8 (3.7-6.3)†	7.0 (5.3-9.2)†
Evolution	17/02/2015	No		0.7 (0.3-1.1)*†‖£	2.8 (2.1-3.5)*†£	
Gemini	07/09/2010	Yes	2007 (AOANJRR)	9.5 (2.5-33.0)*	23.8 (10.7-48.1)*	23.8 (10.7-48.1)*
Genesis	09/05/2006	Yes	2004 (AOANJRR), 2018 (SAR), 2021 (NJR)	1.0 (0.7-1.3)*†	3.6 (3.2-4.1)*†	5.6 (4.8-6.3)*†
GMK Sphere	03/07/2017	No		1.1 (0.9-1.4)*†¥‖£	3.7 (2.9-4.5)*†¥£	4.3 (2.4-6.1)*
Innex	25/07/2005	No		0.9 (0.5-1.3)§¥‖	2.8 (2.0-3.6)ǂ§¥‖	3.5 (2.4-4.6)§
iTotal	23/07/2012	No		0.4 (0.2-0.9)¥	3.5 (2.5-5.0)¥	
Journey	03/01/2014	Yes	2009 (AOANJRR), 2018 (SAR), 2019 (SIRIS), 2014 (NJR)	1.6 (0.1-3.1)*†¥	6.3 (1.8-10.8)*†¥	11.0 (9.9-12.2)*
Kinemax	14/05/2015	Yes	2006 (SAR)			
K-mod	19/05/2014	No				
LCS	02/12/2005	Yes	2012 (AOANJRR), 2021 (NJR)	0.9 (0.2-1.6)*†	5.6 (1.8-9.5)*†	7.7 (2.5-12.8)*†
Legion	22/08/2009	Yes	2017 (AOANJRR), 2019 (SAR)	3.3 (2.3-4.6)*	6.3 (4.8-8.3)*	9.9 (7.5-13.0)*
METS Smiles	17/08/2016	Yes	2018 (NJR)			
MRK	31/12/2021	No		0.3 (0.0-0.6)*†§	1.8 (1.2-2.3)*†§	3.1 (1.6-4.6)*†
Multigen	12/05/2021	No				
Mutars	03/04/2013	Yes	2023 (AOANJRR)	6.5 (4.2-9.9)*		
Natural-knee	07/11/2019	No		0.4 (0.2-0.7)*§‖£	1.7 (1.2-2.1)*§‖£	3.2 (2.4-3.9)*§

Nexgen	13/09/2004	Yes	2018 (AOANJRR), 2015 (SAR)	2.4 (1.9-3.2)[*]	5.0 (4.2-6.1)[*]	6.9 (5.1-9.2)[*]
Noiles	02/03/2014	Yes	2018 (NJR)			
Optetrak	01/06/2006	Yes	2007 (AOANJRR)	1.0 (0.0-2.1)[*]	10.3 (4.1-16.4)[*]	13.7 (7.0-20.4)[*]
Persona	21/11/2012	Yes	2021 (SAR)			
PFC Sigma	02/12/2005	Yes	2018 (AOANJRR), 2012 (SAR)	2.2 (1.1-4.6)[*]	7.1 (4.7-10.5)[*]	7.4 (5.0-10.9)[*]
Physica	18/04/2019	Yes	2019 (SIRIS)	1.7 (1.3-2.3)[¥]	6.8 (5.9-7.9)[¥]	
Saiph	25/03/2022	No		0.6 (0.3-1.0)[ǂ]	1.4 (0.9-2.0)[ǂ]	
Score	04/10/2019	Yes	2013 (AOANJRR)	1.5 (0.8-2.2)[*]	6.5 (5.5-7.6)[*]	11.1 (9.3-12.8)[*]
Scorpio	26/08/2005	Yes	2014 (AOANJRR)	1.2 (0.7-2.0)[*]	6.1 (4.9-7.7)[*]	7.4 (6.0-9.2)[*]
TC-plus	10/06/2008	Yes	2008 (AOANJRR)	1.6 (0.2-10.7)[*]	8.4 (3.6-19.1)[*]	14.4 (7.4-26.9)[*]
Triathlon	07/02/2007	Yes	2021 (SAR)			
Unity	30/09/2021	No		0.4 (0.1-0.9)[*ǂǁ]	1.5 (0.7-2.3)[ǂǁ]	
Vanguard	17/11/2016	Yes	2012 (AOANJRR), 2009 (SAR)	1.9 (1.2-2.6)[*]	5.9 (4.7-7.1)[*]	8.2 (6.8-9.5)[*]

[*] = based on revision risks (RR) as reported by the AOANJRR; [†] = based on RR as reported by the NJR; [ǂ] = based on RR as reported by the RIPO; [§] = based on RR as reported by the LROI; [¥] = based on RR as reported by the SIRIS; [ǁ] = based on RR as reported by the EPRD; [£] = based on RR as reported by the AJRR. TK = total knee; CI = confidence intervals; AOANJRR = Australian Orthopaedic Association National Joint Replacement Registry; SIRIS = Swiss National Hip & Knee Joint Registry; SAR = Swedish Arthroplasty Register; NJR = National Joint Registry for England; Wales, Northern Ireland, the Isle of Man and Guernsey.

Table 5. *Total knee implants brand names with at least one safety notice*

IMDRF code	TK implants (n=26) in the "both" group	TK implants (n=12) in the "safety notices only" group
A01		4 (6.7)
A02	313 (43)	26 (44)
A04	56 (7.7)	7 (12)
A05	41 (5.6)	
A09	6 (0.8)	
A17	59 (8.1)	
A18	9 (1.2)	1 (1.7)
A20	2 (0.3)	
A21	70 (10)	11 (19)
A23	113 (16)	6 (10)
A24	34 (4.7)	1 (1.7)
A26	25 (3.4)	3 (5.1)
Total	728	59

Table 6*. IMDRF medical device problem codes described in safety notices. Values are count (%)*

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