IMDRF International Medical Device Regulators Forum

Final Document

Title: Tools for Assessing the Usability of Registries in Support of Regulatory Decision-Making

Authoring Group: Patient Registries Working Group

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Table of Contents

Preface

The document herein was produced by the International Medical Device Regulators Forum (IMDRF), a voluntary group of medical device regulators and experts from other sectors of the medical device ecosystem from around the world. The document has been subject to consultation throughout its development.

1.0 Introduction

Registries (including registry consortia and strategically coordinated registry networks -CRNs) are critical data infrastructure for capturing outcomes associated with medical device use, and as such continue to demonstrate an impact on the quality of clinical care worldwide. In 2014 the International Medical Device Regulators Forum (IMDRF) identified a significant gap in optimal use of registries for regulatory decision making. This led to the creation of IMDRF Registry Working Group that produced two documents to guide alignment and use of registries generated data with regulatory decision making needs; (1) Principles of International System of Registries Linked to Other Data Sources and Tools, (2) Methodological Principles in the Use of International Medical Device Registry Data.

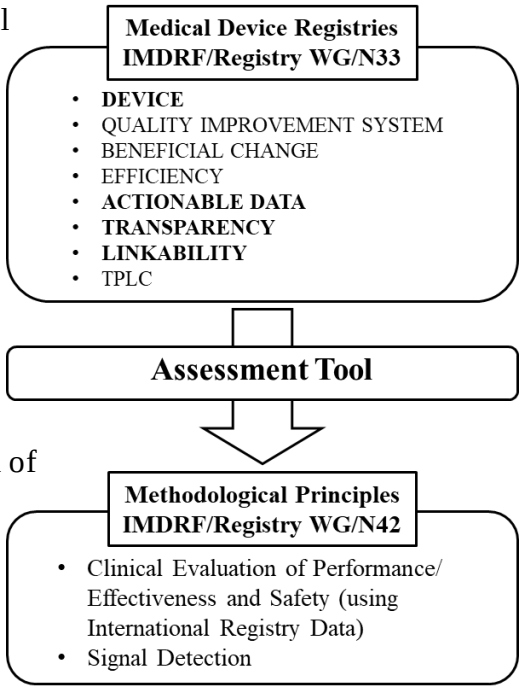

Figure 1. IMDRF Context: Relationship Between the Registry Documents

In the first document on Principles of International System of Registries Linked to Other Data Sources and Tools, the registry system was defined and eight registry qualifiers were identified to enhance its impact and sustainability (Figure 1). The Second document provides guidance on Methodological principles in the clinical evaluation of performance/effectiveness and safety across the device lifecycle using international Coordinated Registry Network via iCRNs.

2.0 Scope

The purpose of this document is to provide guidance to regulators of medical devices, registry organizations and other interested parties on the use of registry-generated data in support of regulatory decisions. Such decisions include (a) initial device approval (when applicable), (b) expanded/broadened indications, (c) post-market studies, (d) post-market surveillance, (e) development of objective performance criteria (OPCs)/performance goals (PGs) and (f) device tracking; and (g) field safety correction actions.

This document identifies key processes and features to be considered in assessing the usability of registry data for regulatory purposes, encompassing both (a) data produced by registries and (b) data produced by registry linkability to other sources (including other registries) to enrich the evidence available for regulatory decision-making. These assessment elements are intended to apply to both (a) purpose-built medical device registries (including those sponsored by manufacturers) and (b) other types of patient registries (e.g. quality registries), such as those that assemble data on surgical procedures that have a potential to generate data about medical devices.

The authors of this document recognize that data produced by a registry may be suitable for making one type of regulatory decision but not others. Individual country regulators are expected to both (a) assess independently the suitability of registry-generated data for regulatory purposes and (b)

decide what actions to take based on applicable national and regional regulations. The assessment elements identified in this document do not constitute a checklist of requirements to certify registry organizations or to assign numerical quality ratings to registry-produced data. If, based on use of the assessment elements contained in this document, regulators find that checklist may be useful, additional work will be required to produce a robust assessment tool.

This document is intended (a) to promote convergence of regulatory approaches, (b) to enhance the technical capabilities of medical device regulators and other ecosystem stakeholders, and (c) to accelerate evidence generation. It may be useful to registry organizations that want their data to be considered in regulatory decision-making. The stakeholders are encouraged to compare elements discussed in this document to their current processes and consider closing any evidence gaps that are found. This document may also be helpful to manufacturers of medical devices that want to include registry-generated data in their regulatory applications.

In summary, the use of the assessment elements described in this document is expected to promote consistency, predictability, and transparency in maximizing the utility of real-world data in the evaluation of (a) medical device safety, effectiveness, and reliability and (b) patients' acceptance of and satisfaction with medical devices. We anticipate that such increased acceptance and satisfaction will primarily be driven by two factors. These are the additional transparency achieved via implementation of the objective assessment tool, and the additional incorporation of patient reported information captured in many registries that would now have an easier path towards use in regulatory decisions.

A clear process for further leveraging of patient relevant information in a transparent fashion can reasonably be expected to increase acceptance and satisfaction with medical devices by patient.
The proposed area of emphasis for the assessment in the Appendix 1 is intended to provide expectations of the acceptable levels of key registry attributes/elements for various regulatory uses.

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3.0 Definitions

Lifecycle: All phases in the life of a medical device, from the initial conception to final decommissioning and disposal (ISO 14971:2007).

Medical Device Registry: An organized system that continuously and consistently collects relevant data in conjunction with routine clinical care, evaluates meaningful outcomes, and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (e.g. international, national, regional, and health system) with a primary aim to improve the quality of patient care (Principles of International System of Registries Linked to Other Data Sources and Tools, IMDRF/Registry WG/N33FINAL: 2016;

Signal detection: The process of determining patterns of association or unexpected occurrences that have the potential to impact patient management decisions and/or alter the known benefit-risk profile of a device (Methodological Principles in the Use of International Medical Device Registry Data, IMDRF/Registry WG/N42FINAL: 2017).

4.0 Elements for Assessment of Registry for Regulatory Uses

There are multiple and often mutually exclusive domains of registries that contribute to their suitability for regulatory decision making including (a) registry organization (that owns or controls the system), (b) registry data management system (the mechanisms that collects and processes data), (c) registry data quality program and registry outputs (e.g. data available to send to regulators). It is possible that specific registry organization will have processes aligned with elements of suggested governance, but the data generated by registry will not be relevant for specific regulatory decision.

I. *Initial approval* (when applicable)*

II. *Expanded/Broadened indication***
III. *Post-market study*
IV. *Post-market surveillance*
V. *Objective Performance Criteria/ Performance Goals - OPCs/PGs*
VI. *Device tracking*
VII. *Field safety corrective actions*

*: Situations where registry data are used for purposes of initial approval are likely to be narrow at present, and include use as a concurrent control group for a clinical trial or for an orphan disease or device.

**: While the clinical data collected in registries can involve unapproved uses of marketed devices ("off-label use"), this document does not explicitly encourage such off-label use beyond that which would occur as part of standard clinical practice. Systematic collection of clinical data involving off-label use should comply with any relevant regulations in a given jurisdiction.

The categories listed above may be partially overlapping, such as with post-market studies and post-market surveillance. Further, the general categories may have variations in definition across disparate regulatory bodies.

These seven categories have different requirements in terms of robustness of registry processes. For example, using registry data to obtain initial approval of indication for the device might require accurate and reliable patient data capture, using robust study designs, at clinically relevant time intervals throughout the appropriate portions of the device lifecycle, and data should be analyzed with appropriate statistical methods for addressing the pertinent scientific questions relevant for the decision making. On the other hand, registry-generated data not used for the primary indication might be able to support broadening the indications for use of already approved devices. Further, registry data may serve as a postmarket control suitable for providing ongoing information for safety surveillance and for effectiveness.

In general, levels of evidence needed to support the regulatory decisions in each use range from the most robust of evidence for initial indications to a less robust level when used to support device surveillance efforts.

The assessment elements described in this document for usability of registries for regulatory decision making builds on the composite of key registry attributes and recommendations identified in the previous IMDRF registry principle documents. These include (a) Device identification (b) Quality and methodological processes leading to actionable data; (c) Transparency/ Governance, and (d) Linkability to other data sources.

4.1 Governance structure and processes

It is important that device registries should have proper governance structures in place in order to ensure that registry conducts/carries out its activities in an appropriate manner, particularly with regard to the handling of information about patients, clinicians, healthcare institutions and manufacturers. This can be achieved by the registry establishing a governance group (e.g. steering committee / board) which sets registry objectives and priorities and which oversees registry activities and processes. The remit of the governance group should be clearly defined and should be publicly stated on the registry website. Membership of the group should also be made known publicly and should include representatives of all key stakeholders including: patients (e.g. via

patient groups); clinicians (e.g. via professional bodies); healthcare institutions; manufacturers (e.g. via trade associations), payers and regulators (device and clinical practice). In all aspects of the registry's work, access to information of a personally or commercially confidential nature should be on a limited basis as appropriate.

4.2 Quality Management System

4.2.1 Legal and Ethical Requirements for Data Collection and Handling

It is important that registries comply with national / regional legal requirements for data collection and handling (data protection). Personal information about patients should be treated as confidential at all stages of registry activity and attention should be given to transmission of any personal data (within the registry, linking to other data sources and to third parties), including on a cross-border basis. Using methods for concealing of personal information should be considered (where appropriate when sharing data) but the methods should not sacrifice longitudinal linkages of individual patient data. The registry should have a documented policy on data collection and handling, which should be agreed by the registry's governance group. As new types of data uses are added, data handling policy should be updated and transparent to the public. Commercial confidentiality should be maintained. Registries should ensure that they do not share data that would lead to misuse or provide a business advantage to one manufacturer over another.

Where consent is required (opt-in / opt-out) the registry should have a specific consent form (or a standardized form of words to be included in the consent documentation for the clinical procedure) which should be published on the registry website along with a clearly worded explanation of the consent requirements and processes. The consent policy should take into account relevant national / regional / international legal requirements including those related to exemption from the need to gain patient consent for data recording and approved by an Ethical Committee / IRB.

The form and explanatory information should be in plain language and it should be made available in relevant official languages of the country / region where the registry operates. The registry should take steps to ensure that all of those involved in the process of obtaining patient consent for their information to be included in the registry are aware of the consent requirements and the registry should monitor that they fulfill these requirements. See for example the consent forms plus associated explanatory leaflets for the UK National Joint Registry - http://www.njrcentre.org.uk/njrcentre/Patients/IntroductiontotheNJR/NJRconsent/tabid/92/Default.aspx

4.2.2 Policy on Conflict of Interest

Conflict of Interest (CoI) potentially influences the collection and analysis of registry data, as well as any decision-making based on such results. As the registry assessment tool is intended to qualify the registry that is utilized to support regulatory decision-making, it is critically important to understand the management of CoI of the registry should have a policy on the management and disclosure of CoI, which should be agreed to by the registry governance structure and which should be published on the registry's website). When the data is utilized by stakeholders for assessing the

performance of the device, and safety surveillance, members of the Committees or other registry related personnel such as statisticians, epidemiologists, data managers who have a conflict of interest must be excluded from the analysis team. When requested by the stakeholder including the regulatory authority, the information covered by CoI policy information should be available especially if the data or results of analysis are used to support regulatory decision.

4.2.3 Policy on Access to Data

The registry should develop a policy and establish procedures governing data access and use. Such policy should identify, for each relevant stakeholder (depending on intended use of the data) the appropriate level of data access. Data stored in the registry should be maintained in the data repository after the data cleaning is conducted. Any change of data must be recorded in the entry log. After cleaning, the data may be accessed by the stakeholders including manufacturer, regulatory authority as well as academic or professional societies upon request. Any request should be reviewed and approved by the data utilization committee (when established) or by the steering committee which determines the appropriateness of the request for data access and use. Since data may include the patient level information and unique device identification information depending upon the nature of the assessment, confidentiality should be maintained. Registry data should be accessible to regulatory bodies in support of regulatory decision-making (e.g., regulators may request data for their analysis, auditing etc).

4.2.4 Essential Information Available for Verification by Relevant Authority

Regulatory bodies should be able to verify essential information needed for their decision making. Registries contact information and processes to support data verification should be readily available. Any clinical data used for regulatory processes should be disclosed and can be subject to audit, if the information available in regulatory submission does not cover all relevant questions concerning validity and reliability.

4.3 Data gathering

The data collection procedures used for registries should be clearly defined and described in a detailed data management standard operating procedures (SOP) manual. The records regarding the assessment of adherence to the registry' s established data quality assurance and quality control policies and procedures, the quality of data element population (e.g., whether abstracted from a verifiable source to assess transcription errors or automatically populated through a data extraction algorithm). Summary information related to management and data quality check process should be publicly available describing how potential confounders due to incomplete documentation or data handling processes are managed.

4.3.1 Relevant Variables

Registries are usually established for non-regulatory purposes (e.g. improvement of clinical care). Therefore, regulators should carefully assess whether the individual variables collected by the registry are sufficient in the number and scope to be used for regulatory purposes. For analysis and interpretation of registry generated data, it is important to have a common set of data elements, a

common definitional framework (i.e., data dictionary), and pre-specified time intervals for data element collection and outcome analyses.

The recommended minimum set of variables (case report form or data collection tool) should satisfy regulatory purpose / decision making, clinical area of interest and study design employed to address particular questions. In general, the list of variables should include demographic factors, medical history / co-morbidities, procedure / device information, operators / physicians, follow-up information, and outcomes of interest.

Registries intending to contribute data for regulatory purposes should be able to document the following information:

- The overall percentage of patient exposure to the device that are captured in the registry and representativeness of the registry population to the treated population;
- The extent to which exposed patients within the scope of the registry are actually consecutively captured (i.e., minimization of selection bias);
- Extent of follow-up available at important durations of times following the index procedure; if inadequate, ability to link to additional datasets may potentially be a good surrogate;
- Qualifications of data entry personnel if direct data quality/validation is not possible;
- Adherence to source verification procedures and data collection and recording procedures for completeness and consistency;
- Completeness (i.e., minimized missing or out of range values) of data necessary for specified analyses, including variables required for adjustment/confounding factors;
- Data consistency across sites and over time;
- Evaluation of on-going training programs for data collection and use of data dictionaries at participating sites;
- Evaluation of site and data monitoring practices;
- Identify sources of data if other than data entry;

4.3.2 Device Identification

Being able to unambiguously identify the device(s) associated with each registry record is crucial if outputs from the analysis of registry data are to be used to underpin regulatory decision. The IMDRF guidance on "Principles of International System of Registries Linked to Other Data Sources and Tools" (IMDRF/REGISTRY WG/N33FINAL:2016 – 30 September 2016) identifies eight qualifiers which define the impact, value, and sustainability of the medical device registry. The first of these relates to device identifiers and states that:

The registry contains sufficient information to uniquely identify the device. Ideally, the unique device identifier would be included, but when the UDI is not available, the registry would include a combination of identifiers (catalogue number, manufacturer, and description) that, in combination, will assist in uniquely identifying the device.

The most effective way to achieve unambiguous device identification is to use a recognized Unique Device Identification (UDI) system; international guidance on UDI systems is given in the IMDRF UDI guidance (IMDRF/WG/N7FINAL:2013 UDI Guidance - 9 December 2013).

UDI systems based on the IMDRF guidance have been introduced on a regional basis in recent years, for example in the US (21 CFR Parts 16, 801, 803, et al - Unique Device Identification System; Final Rule - 24 September 2013) and Europe (Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 Article 27). Systems such as these (if available) should be used by registries as the primary device identification.

For each procedure, registries should systematically record:

- Device identifiers (UDI-DI) e.g. GS1 GTIN (Global Trade Item Number) or HIBC-LIC (Labeler Identification Code) or ISBT 128-PPIC (Processor Product Identification Code)
- Production identifiers (UDI-PI) e.g. device serial number or batch/lot number

Ideally the collection of this information should be embedded in the health care delivery system so that data collection occurs as part of care delivery and is integrated with work flow of the clinical teams involved in the delivery of care. This can be achieved by scanning the barcodes on the device labels into the hospital electronic record systems at the point and time of use for onward (semi-automated) transmission to the registry. Adopting such an approach optimises data recording efficiency and accuracy, and should lead to more complete and reliable registry records.
Where UDI is not available a combination of identifiers should be adopted to unambiguously identify devices. These may include the following:

- Manufacturer
- Medical Device Name (Brand/Trade/Proprietary or Common name)
- Model
- Device catalogue / reference code (REF)
- Device serial number (preferred, if applicable)
- Device batch or lot number

For definitions of the above terms see: IMDRF/RPS WG/N19 FINAL: 2016 – 24 March 2016.

4.3.3 Internationally recognized standards

Registries should adhere to internationally / nationally recognized standards and harmonization of the CDM (Common Data Models. For example, in the United States several common data models are harmonized nationally (OMOP, Sentinel / PCORNet etc.). To advance medical device evaluation, Medical Device Epidemiology Network (MDEpiNet) pioneered the international harmonization of disease specific-clinically relevant common data models. Specifically, International Consortium of Orthopedic Registries (ICOR) data model for joint replacement was among the first, and International Consortium of Vascular Registries (ICVR) is now developed. This is particularly important in anticipation of evolving international convergence efforts (including reporting methodologies).

4.3.4 Linkability

Most procedural or device registries have limited follow up data on outcome events but often have rich clinical information about the patients and procedures. Linkage of these registries with other,

complementary data sources (e.g. subsequent health care encounters, short term complications, long-term outcomes) would yield enriched data source for regulatory purposes. In addition, linkage is often used for validation processes of registries. Complementary data may include but are not limited to other registries, national death records, electronic medical records, or longitudinal administrative claims/discharge databases. Linkability might depend on the limitations within national legal context.

There are two broad methods of data linkage:

(a). Deterministic (direct)

Deterministic linkage algorithms aim to determine if record pairs agree or disagree on available set of identifiers and when agreement on a given identifier is assessed as a distinct "all-or-nothing" outcome (Dusetzina SB, Tyree S, Meyer AM, et al. Linking Data for Health Services Research: A Framework and Instructional Guide).

(b). Probabilistic (indirect)

Probabilistic approaches to link large datasets aim to use limited identifiers applied methodologically in a way that maximizes the probability that a data field agrees given a record pair matches, minimizes the probability that a data field agrees given a record pair is unmatched, and provides greater precision from non-uniformly distributed fields (Jaro MA). Probabilistic linkage of large public health data files). It is a method that enables the combination of record information in different data sets to form a new linked dataset. It has been described as a process that attempts to link records into different files that are most likely to belong to the same person / organization. The probabilistic link uses several identifiers, in combination, to identify and evaluate links. Probabilistic binding is usually used when a unique identifier is no available or is of insufficient quality (Australian Government, National Statistical Service, Data Linking). Also of note is that the UDI can help with probabilistic matching, but by itself does not accomplish deterministic matching unless the device is serialized.

In assessment of the usability of a registry for regulatory uses we assume that deterministic linkage is possible and is applied because direct identifiers (patient names and exact birth date, or unique health system identifier) are available in both registry and in the linkable database, and the data on these identifiers is of good quality. The probabilistic method is applied when direct identifiers are unavailable or identifiers are not reliable.

Both matching approaches have their strengths and their limitations. It is generally recommended to evaluate the probability of successful matching as a rule, and then employ a combination of deterministic and probabilistic methods that optimizes the combination of completeness of the population and accuracy of matching.

4.3.5 Data Storage / Processing (Security Protection against hacking, altering, deleting or steeling data)

The registry should develop a policy and establish procedures governing data storage and processing. Such policy should identify the requirements and procedures to protect the registry data against hacking, altering, deleting or steeling of the data stored in the registry.

4. 4. Methodologies Leading to Actionable Data

Processes applied to registry data, such as analysis and risk adjustment modeling and inferences, can have a fundamental impact on conclusions drawn. A previous IMDRF Document "Methodological Principles in the Use of International Medical Device Registry Data" has outlined core methodological aspects Methodological Principles in the Use of International Medical Device Registry Data, IMDRF/Registry WG/N42FINAAL: 2017.

The data elements available for analysis should be capable of addressing the specific question of interest to regulators when valid and appropriate analytical methods are applied. The distinction should be made between the elements that all registries would share and the specifics needed in each specialty areas. The role of specialty societies and organizations in countries will continue to be critical and need to be coordinated internationally as well as elements of all use (social and demographic elements). Modular add-on data (prospective trials) or links to data from other sources (retrospective data) when additional granular data not included in the standard registry dataset is needed for regulatory decision to be possible

4.5 Interpretation

The meaning of the results should be described by experts to various stakeholders (e.g. potential changes to indications, practice etc). Registries should consider 1) to disseminate information to various stakeholders who need to know it in an effective manner and user-friendly format and 2) to gather feedback on information's utility.

4.6 Transparency / Display/ Distribution

It is now widely recognized that transparency is an increasingly important aspect of healthcare provision and management. See for example the introduction to the European Medical Device Regulations) which includes the following (Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 recital 45):

> *Transparency and adequate access to information, appropriately presented for the intended user, are essential in the public interest, to protect public health, to empower patients and healthcare professionals and to enable them to make informed decisions, to provide a sound basis for regulatory decision-making and to build confidence in the regulatory system.*

Registry transparency and governance reflect a wide variety of real world situations. Selected considerations of direct relevance to the document's purposes are discussed here and only in relevant details.

The need for appropriate transparency in all aspects of registry activities should be taken into account by those maintaining the registries. Transparency is enhanced through the establishment and continuously maintenance of a publicly accessible website that: (a) describes the aims of the registry; (b) includes key information about governance processes; (c) explains how to participate in the registry; and (d) discloses how the registry is funded. The need for transparency should be balanced by the need to maintain confidentiality with regard to identifiable information about patients, clinicians and devices.

It is important to enhance the objective of the registry reports especially with reference to the correlations with the vigilance (see the reference to the safety signals on implant deficiency). The reports published by the registries are recommended to include the number of devices used, overall percentage of patient exposure to the device that is captured in the registry, representativeness of the registry population to the treated population, patient demographic data (presented as aggregated data), procedure related information, major outcomes captured in the registry and via linkage, and methods used to generate results.

Publication of data should respect the national / international rules for data protection. The reports should contain the results of the preliminary and final assessment of the accumulated data including the adjusted analyses. The information regarding device-related adverse events should be reported in conjunction with the report to the manufacturer, physicians, and regulatory agencies. It is recommended that reports are published annually using agreed upon format. The methodology applied for the adjusted analyses should be available to regulators upon request.

Websites are important tools for informing all stakeholders concerning various aspects of a registry, their internal processes, and findings identified safety signals on implant deficiency or limitations of their evaluations. The registries should be encouraged to take proactive use of this opportunity. Annual Reports as well as scientific publications (e.g., peer reviewed publications or practice guidelines) use of the registry source for determining outcomes-based quality assessments, validated predictive risk modeling, signal detection, performance improvement, benchmarking, and other clinically-meaningful uses.

5.0 APPENDIX 1: Proposed Areas of Emphasis for an Assessment of Regulatory Use

ELEMENTS	REGULATORY CATEGORIES						
	Initial Approval*	**Broadening Indication****	**Post market study**	**Postmarket Surveillance**	**Development of OPC/PG**	**Device Tracking**	**Field Safety Corrective Actions**
Governance							
Governance structure and process	XX	XX	XX	X	XX	X	X
Quality Management System							
Legal requirements for data collection/handling	XX	XX	XX	X	XX	X	X
Information on Patient Data Protection (e.g. if Exempt from consent, Opt-out, Opt-in)	XX	XX	XX	X	XX	X	X
Policy on access to data	XX	XX	XX	XX	XX	X	X
Essential information available for verification by relevant authority (e.g. competent authority, notified body)	XX	XX	XX	XX	XX	XX	XX
Data Gathering							
Relevant Variables	XX	XX	XX	XX	X	X	X
Unambiguous Device Identification (preferably internationally recognized UDI system)	XX	XX	XX	X	X	X	X
Linkability (Registry with other data source):							
Deterministic	XX	X	X	X	X	X	X

Probabilistic	NR	X	X	X	X	X	X
Use of Controlled Vocabularies	XX	XX	XX	X	X	X	X
Use of nationally/internationally harmonized minimum data model	X	X	X	X	X	X	X
Data Storage							
Security Protection against hacking, altering, deleting or stealing data	XX	XX	XX	XX	XX	XX	XX
Methodologies Leading to Actionable Data							
Conduct of analyses across different types of analysis frameworks	XX	XX	XX	XX	XX	X	X
Data Interpretation	XX	XX	XX	XX	XX	X	X
Transparency/ Display/ Distribution							
Report; Key elements and frequency of reports	X	X	X	X	X		
Website and web-reporting	X	X	X	X	X	X	

Legend

XX - Highly Recommended
X - Recommended
☐ - *Optional*
NR- Not Recommended

*Situations where registry data are used for purposes of initial approval are likely to be narrow at present, and include use as a concurrent control group for a clinical trial or for an orphan disease or device.

**While the clinical data collected in registries can involve unapproved uses of marketed devices ("off-label use"), this document does not explicitly encourage such off-label use beyond that which would occur as part of standard clinical practice. Systematic collection of clinical data involving off-label use should comply with any relevant regulations in a given jurisdiction.

IMDRF International Medical Device Regulators Forum

PROPOSED DOCUMENT

International Medical Device Regulators Forum

Title: Definitions for Personalized Medical Devices

Authoring Group: IMDRF Personalized Medical Devices

Date: 26 March 2018

Table of Contents

Preface

The document herein was produced by the International Medical Device Regulators Forum (IMDRF), a voluntary group of medical device regulators from around the world. The document has been subject to consultation throughout its development.

1.0 Introduction

The purpose of this IMDRF guidance is to establish harmonized definitions that are used to describe medical devices that are intended for a particular individual. The adoption of consistent, harmonized definitions for such medical devices could underpin a harmonized regulatory approach for controls on these devices and offer significant benefits to the manufacturer, user, patient, and to Regulatory Authorities. Eliminating differences between jurisdictions supports global convergence and decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments.

Technology has progressed from the time the original GHTF foundation documents were published. It is now possible to produce medical devices that are individualized, for example, using additive manufacturing (3D printing) methods based on patient CT scans, on a commercial rather than artisanal scale. The original GHTF documentation does not adequately address devices of this nature.

Many jurisdictions already define the term custom-made device and have introduced exemption provisions for regulating custom-made medical devices with the intention to cover special cases where commercially available mass produced products are inadequate for the needs and requirements of a particular patient. In some jurisdictions, the exemption provisions were based on the premise that affected devices would largely comprise low risk products or limited use of higher risk implantable devices. In other jurisdictions the exemption provisions were established with the intention that numbers of custom-made devices would necessarily be small, due to the requirement for them to be used only in special cases.

Now regulators are faced with a very different environment. Technology has made “custom-made” devices, including implantable devices for particular patients, within reach on a much greater scale. Consequently, some jurisdictions are noticing inappropriate use of custom-made device exemptions; with growing numbers of patients receiving higher risk classification medical devices to meet their particular needs, under these exemptions.

2.0 Scope

This document applies to all medical devices, and is intended to identify and describe different categories of devices that are produced for the use of a particular individual, and also to define some other terms that are relevant to defining these types of devices.

3.0 References

GHTF/SG1/N68:2012 *Essential Principles of Safety and Performance of Medical Devices*

GHTF/SG1/N78:2012 *Principles of Conformity Assessment for Medical Devices.*

GHTF/SG1/N70:2011 *Label and Instructions for Use for Medical Devices.*

GHTF/SG1/N071:2012 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*

GHTF/SC/N4:2012 *Glossary and definition of terms used in GHTF documents*

IMDRF/SaMD WG/ N10 FINAL:2013 *Software as a medical device (SaMD): Key Definitions*

ISO/ASTM 52900:2015 *Additive manufacturing — General principles — Terminology*

Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices

USFDA CDRH, Technical Considerations for Additive Manufactured Devices - Guidance for Industry and Food and Drug Administration Staff, 5 Dec 2017

USFDA CDRH, Custom Device Exemption - Guidance for Industry and Food and Drug Administration Staff, 24 Sept 2014

4.0 Definitions

4.1 **personalized medical device –** a generic term to describe any of the types of devices that are intended for a particular individual, which could be either a **custom-made**, or **adaptable**, or **patient-specific** medical device.

4.2 **custom-made medical device –** a medical device that, at a minimum, meets the following requirements:

- it is intended for the sole use of a particular individual; and
- it is specifically made in accordance with a written request of an authorized healthcare professional, which gives, under their responsibility, specific design characteristics; and
- it is intended to address the specific anatomo-physiological features or pathological condition of the individual for whom it is intended.

Note 1: **patient-specific medical devices, adaptable medical devices** and **mass-produced** medical devices made by means of industrial manufacturing processes in accordance with the written request of an authorized healthcare provider, shall not be considered to be custom-made.

Note 2: 'Specific design characteristics' means unique design specifications that are based on an individual's specific anatomo-physiological features or pathological condition, and that cannot be proposed by a manufacturer without the involvement of a healthcare professional during the conception phase. (For example, transmitting only dimensions/geometric parameters (such as DICOM files from CT scans) to a manufacturer prior to the production of a medical device is not sufficient to be considered as giving specific design characteristics.)

4.3 patient-specific or patient-matched medical device – a medical device produced by a manufacturer based on a standard device template model, or specified design envelope (e.g., minimum and maximum dimensions, mechanical performance limits, and other clinically relevant factors), that is matched to a patient's anatomy using techniques such as scaling of the device based on anatomic references, or by using the full anatomic features from patient imaging, and which is produced through a process that is capable of being validated.

4.4 adaptable medical device – a mass-produced medical device that must be adapted or assembled at the point of care, in accordance with the manufacturer's validated instructions, to suit an individual patient's specific anatomo-physiologic features prior to use.

4.5 mass-produced medical devices –identical medical devices that are produced in continuous production runs or homogenous batches**.**

Note: A batch is considered homogeneous when equivalent parts or materials are manufactured and/or tested in the same manner, without interruption, typically on the same day or in the same time period, and produced by the same person, or with the same machine/equipment set-up and fulfill the same specifications [Ref *MEDDEV* 2.5/6 Rev. 1 http://ec.europa.eu/DocsRoom/documents/10287/attachments/1/translations].

Appendix

Appendix – Examples of personalized devices

Custom-made medical devices

- An orthopedic implant requested by an orthopedist that, in addition to DICOM files, sends to a 3D printing implant manufacturer specific requirements for rigidity/flexibility that the implant must present in specific locations, due to the unique pathology/condition of the patient.

- Artificial cervical disc replacement, with features specified by a spinal surgeon, for reconstruction of the cervical disc following cervical discectomy to treat cervical radiculopathy in a 7’2” male patient. In this scenario, the osseous dimensions of this patient's cervical spine exceed those which an available artificial cervical disc would accommodate.

Patient-specific medical devices

- Cutting guides used in procedures such as knee arthroplasties, or guides used for pedicle screw placement, that are made by 3D printing based on MR or CT data to match a specific patient.

- Plates used to fix a broken bone, which are made by 3D printing, based on a template model and DICOM files/ images of the patient. The plates are printed within the validated dimensional ranges allowed by the specified design envelope.

- Prostheses produced by a 3D printing manufacturer, from a template model and DICOM files transmitted by an authorized person

- Acetabular guide designed to assist a surgeon with pre-operatively planned placement of the acetabular cup component of a total hip replacement. Under a surgeon’s guidance, the guide may be based upon MR or CT images of a patient’s specific anatomy and pre-operatively planned placement of the acetabular cup. The device, as well as the pre-operative planning process upon which the design of the patient-specific guide is based, is validated within a certain range of anatomical parameters.

Adaptable medical devices

- Thoracolumbar pedicle screw system, which consists of multiple components from a single manufacturer, that allows the surgeon to build an implant system to fit the patient’s anatomical and physiological requirements in accordance with instructions provided by the manufacturer. This assembly may consist of a combination of hooks, screws, longitudinal members (e.g., plates, rods, plate/rod combinations), transverse or cross connectors, and interconnection mechanisms (e.g., rod-to-rod connectors, offset

connectors). Additionally, longitudinal members may require intraoperative contouring, as intended by the manufacturer, in order to fit the individual patient's spinal curvature.

- Mass-produced polymer surgical implants for cranial reconstruction that are supplied sterile and are intended to be thermoformed during the surgical procedure. The instructions for use provide details for heating and shaping the implant to suit a patient's particular anatomy.

- Mandibular advancement orthosis against snoring and apnea, which is adapted to the dentition through thermoforming, and is adjusted by the patient.

Home
About IMDRF
Work items
Consultations
Documents
Meetings
Stakeholders
Safety information
Recent updates
GHTF Archive

Optimizing Standards for Regulatory Use

A Proposed Document has been released by the International Medical Device Regulators Forum (IMDRF) Standards Working Group.

This consultation will close on Thursday **24 May 2018**.

Working Group Chair: Scott Colburn, USA

Thank you for your contribution aiming at the validation of the IMDRF document.

Consultation documents

N51 - Optimizing Standards for Regulatory Use (PDF 756kb)

N51 - Optimizing Standards for Regulatory Use (DOCX 986kb)