Regulatory Science Symposium

Principles of Global Clinical Research for Medical Devices

Friday, April 9, 2021 / 9am - 3pm PST

Asia-Pacific Economic Cooperation | USC School of Pharmacy International Center for Regulatory Science | SC CTSI

9:00 AM PST	**Introduction** *Eunjoo Pacifici, PharmD, PhD* USC, SC-CTSI, School of Pharmacy I Chair & Associate Professor, Dept. of Reg. & Quality Sciences l Associate Director, DK Kim lnternational Center for Regulatory Science
9:30 AM PST	**Clinical Investigation: Value and Key Aspects of the IMDRF Guidance Document** *Maria E. Donawa, MD* President, Donawa Lifescience Consulting
10:15 AM PST	**Break**
10:30 AM PST	**Good Clinical Practices and ISO 14155** *Danielle Giroud, RN, MBA* Founder, CEO, MD-Clinicals
11:15 AM PST	**General Discussion**
11:30 AM PST	**Lunch**
12:30 PM PST	**From Clinical Data to Clinical Evidence** *Cheryl Hergert, MPH* Principal Clinical Quality Specialist, Medtronic
1:15 PM PST	**Break**
1:30 PM PST	**Developing Clinical Evaluations** *Evangeline Loh, PhD, RAC (US, EU)* Global Regulatory Manager, Emergo by UL
2:15 PM PST	**Panel Discussion**
2:45 PM PST	**Wrap-Up** *Eunjoo Pacifici, PharmD, PhD* USC, SC-CTSI, School of Pharmacy I Chair & Associate Professor, Dept. of Reg. & Quality Sciences l Associate Director, DK Kim lnternational Center for Regulatory Science

Please complete the course evaluation survey at the end of the symposium to receive a certificate of completion. Hours may be eligible for SoCRA and/or ACRP credit.

Series sponsored by The Greater LA CTSA Consortium

UCLA CTSI | SC CTSI | UC IRVINE ICTS from lab to life.

SC CTSI is part of the Clinical and Translational Science Awards (CTSA) , a national network funded through the National Center for Advancing Translational Sciences (NCATS) at the NIH (Grant Number UL1TR001855). Under the mandate of "Translating Science into Solutions for Better Health," SC CTSI provides a wide range of services, funding, and education for researchers and promotes online collaboration tools such as USC Health Sciences Profiles .

Regulatory Science Symposium:
Principles of Global Clinical Research for Medical Devices
Speaker Bios

Eunjoo Pacifici (PharmD, PhD) is Chair and Associate Professor of Regulatory and Quality Sciences and Associate Director of the International Center for Regulatory Science. Dr. Pacifici received a BS in Biochemistry from the University of California Los Angeles and PharmD and PhD in Toxicology from the University of Southern California. She conducted her graduate research in the laboratory of Dr. Alex Sevanian in the Institute for Toxicology where she studied the mechanism of oxidative damage and repair in endothelial cell membrane. Before returning to USC as faculty, Dr. Pacifici worked at Amgen and conducted clinical research with a special focus on Asia Pacific and Latin America. She initially worked in the clinical development group managing U.S. investigational sites and central laboratories, then in the Asia Pacific/Latin America group interfacing with local clinical and regulatory staff in Japan, the People's Republic of China, Taiwan, and Mexico. She represented regional clinical and regulatory views on therapeutic product development teams and led satellite task forces to align local efforts with U.S. activities. Her professional experience includes community pharmacy practice in various settings and clinical pharmacy practice at the Hospital of the Good Samaritan in Los Angeles. Her current focus is on developing the next generation of regulatory scientists and pharmacy professionals with the knowledge, tools, and skills to expedite the development of innovative, safe, and effective biomedical products. epacific@usc.edu

Maria E. Donawa (MD), is President of Donawa Lifescience (headquartered in Rome, Italy) and has over 30 years regulatory experience including six years with the US Food and Drug Administration in medical device regulation. Donawa Lifescience provides clinical services to life science companies worldwide and US and European quality system and regulatory services. Dr. Donawa has assisted a wide range of medical device and IVD medical device companies in complying with European requirements. She is an active member of ISO TC 194 Working Group 4, was responsible for the development and revision of ISO 14155 (Clinical investigation of medical devices for human subjects – Good Clinical Practices) and is a stakeholder observer actively participating in the work of the European Clinical Investigation and Evaluation subgroup of the Medical Devices Coordination Group (MDCG). She has developed expert guidance documents for BSI on clinical data, clinical evaluation, and clinical investigation and a white paper on clinical investigation. For five years, Dr. Donawa served as a registered lead auditor, providing notified body auditing services to a German notified body. For over 25 years until closure of the publication, she was the regulatory columnist for European Medical Device Technology. Dr. Donawa has US degrees in pharmacy and medicine and post-doctoral specialization in clinical and anatomical pathology. medonawa@donawa.com

Danielle Giroud (RN, MBA) is founder and CEO of MD-Clinicals (https://www.md-clinicals.com), a medical device-focused CRO with offices in Switzerland, Frankfurt, and Beijing. Ms. Giroud has over 30 years of experience within the medical device industry. She is an internationally recognized clinical research and regulatory expert, having shared her extensive knowledge and experience with hundreds of multi-national companies, organizations, and start-ups from around the globe to help bring their products to market quickly and efficiently. Ms. Giroud was founder and senior faculty board member of the World Medical Device Organization (https://www.wmdo.org). She was also a convener for the expert group on clinical investigations (TC 194 WG4) for the ISO 14155, and liaison with the EU Commission - Clinical Investigation and Evaluation (CIE) task force and other regulatory authorities throughout the world. dgiroud@wmdo.org

Cheryl Hergert (MPH) is Principal Clinical Quality Specialist at Medtronic overseeing quality and compliance of global clinical operations. With more than 20 years of experience in product development for medical devices, pharmaceuticals and combination products, Ms. Hergert's experience ranges from feasibility to launch with expertise in clinical and regulatory operational management for US and OUS. She holds a Master's in Public Health, and Bachelors in Biochemistry and is currently working towards a Doctorate of Regulatory Science at USC. Her research interests pertain to the use of routine clinical patient health data in clinical research, specifically focusing on the adoption of the use of real-world patient data for regulatory decision making. Cheryl is involved in several global initiatives such as World Health Day and International Women's Day. Through her leadership, World Health Day is celebrated as an annual event at a university level and International Women's Day is celebrated across Medtronic's global enterprise. cherylmhergert@gmail.com

Evangeline Loh (PhD, RAC) is Global Regulatory Manager at Emergo by UL consulting group. During her 14-year plus tenure at Emergo, Dr. Loh has assisted hundreds of manufacturers with global regulatory strategy, registration and consulting projects. Her areas of expertise include European CE marking, clinical evaluation and performance evaluation reports, global vigilance, and device classification in markets worldwide. She has been intimately involved in the transition from the Directives to the Regulations, and all related regulatory requirements. Dr. Loh is a key architect in developing tools for Emergo's Regulatory Affairs Management Suite (RAMS) software. Her previous work experience includes regulatory scientist at Cook Medical and at a non-profit lobbying for medical schools. Dr. Loh holds a PhD in Pharmacology from the University of Texas Health Sciences Center, and a BS in Microbiology from Cornell University and is RAC certified in US and EU. evangeline.loh@ul.com

Regulatory Science Virtual Symposium

Principles of Global Clinical Research for Medical Devices

Introduction

Eunjoo Pacifici, PharmD, PhD
Chair and Associate Professor, Regulatory and Quality Sciences
Associate Director, DK Kim International Center for Regulatory Science

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SC CTSI Clinical Research Support (CRS)

A single stop for accessing all services an Investigator and research team needs to develop, activate, conduct, and report results for human subject research studies

Initial focus on investigator-initiated trials (non-cancer)

- **Services:**
  - Clinical research coordinators for hire
  - Research navigation
  - Recruitment support
  - Budget preparation support
- **Clinical Trials Unit (CTU)**:
  - Skilled research and nursing staff
  - Services to support highly-complexed human subjects research studies
  - Specimen processing lab
- **Voucher program:**
  - Awards up to $3,000 to generate new data for development of clinical and/or community research projects

https://sc-ctsi.org/about/groups/clinical-research-support

Nicki Karimipour, PhD
Program Manager
CRS

Lily Jara, BS
Clinical Research Supervisor
CRS

Contact Information:
crs@sc-ctsi.org

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Monitoring Module

1. Go to: https://uscregsci.remote-learner.net
2. Click ***create new account*** (right-hand side)
3. Type in your information and click ***Create my new account*** (bottom of page)
4. Open your email and click the link to confirm your account
5. Click ***courses*** (middle of page)
6. Scroll down and click ***Module 1 – Clinical Trial Monitoring***
7. Click ***Enroll me*** (middle of page)

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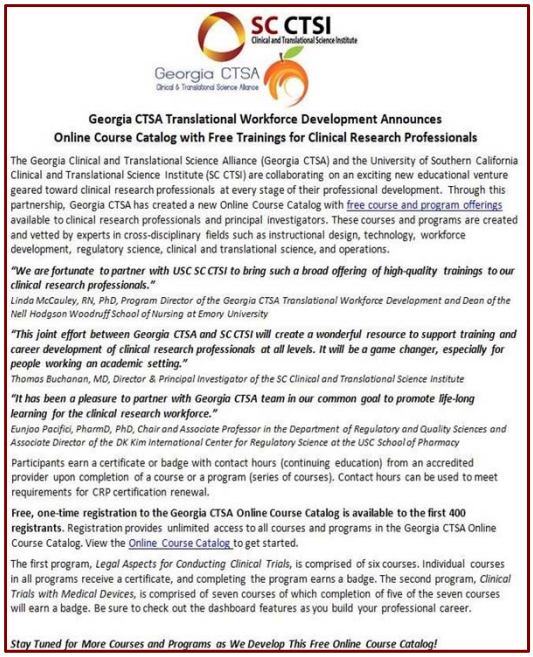
Georgia CTSA and SC CTSI: Online Course Catalog

- Free trainings for clinical research workforce
- Free, one-time registration to the first 400 registrants
- Registration provides unlimited access to all courses and programs in the Online Course Catalog
- Participants earn a certificate or badge with contact hours upon completion of a course or program
- Contact hours can be used for CRP certification renewal
- To get started:

https://twd.ce.emorynursingexperience.com/



SC CTSI Clinical and Translational Science Institute
Georgia CTSA Clinical & Translational Science Alliance

Georgia CTSA Translational Workforce Development Announces Online Course Catalog with Free Trainings for Clinical Research Professionals

The Georgia Clinical and Translational Science Alliance (Georgia CTSA) and the University of Southern California Clinical and Translational Science Institute (SC CTSI) are collaborating on an exciting new educational venture geared toward clinical research professionals at every stage of their professional development. Through this partnership, Georgia CTSA has created a new Online Course Catalog with free course and program offerings available to clinical research professionals and principal investigators. These courses and programs are created and vetted by experts in cross-disciplinary fields such as instructional design, technology, workforce development, regulatory science, clinical and translational science, and operations.

"We are fortunate to partner with USC SC CTSI to bring such a broad offering of high-quality trainings to our clinical research professionals."
Linda McCauley, RN, PhD, Program Director of the Georgia CTSA Translational Workforce Development and Dean of the Nell Hodgson Woodruff School of Nursing at Emory University

"This joint effort between Georgia CTSA and SC CTSI will create a wonderful resource to support training and career development of clinical research professionals at all levels. It will be a game changer, especially for people working an academic setting."
Thomas Buchanan, MD, Director & Principal Investigator of the SC Clinical and Translational Science Institute

"It has been a pleasure to partner with Georgia CTSA team in our common goal to promote life-long learning for the clinical research workforce."
Eunjoo Pacifici, PharmD, PhD, Chair and Associate Professor in the Department of Regulatory and Quality Sciences and Associate Director of the DK Kim International Center for Regulatory Science at the USC School of Pharmacy

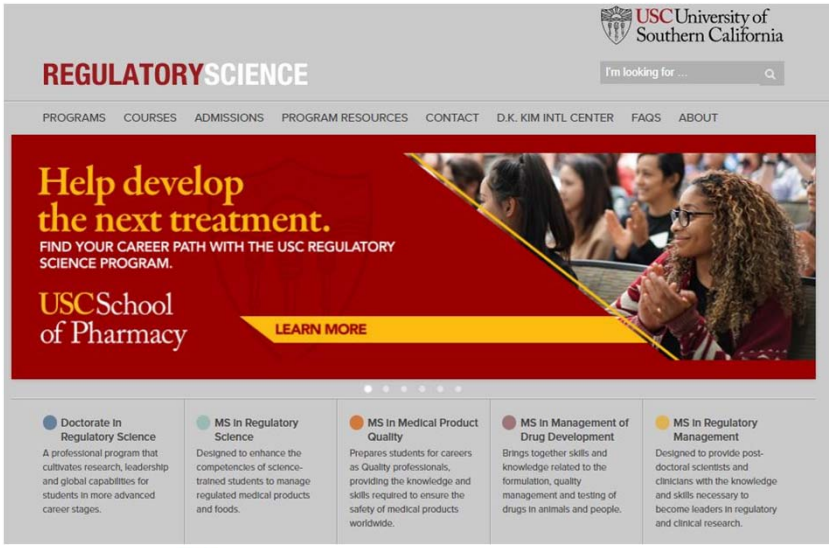
Participants earn a certificate or badge with contact hours (continuing education) from an accredited provider upon completion of a course or a program (series of courses). Contact hours can be used to meet requirements for CRP certification renewal.

Free, one-time registration to the Georgia CTSA Online Course Catalog is available to the first 400 registrants. Registration provides unlimited access to all courses and programs in the Georgia CTSA Online Course Catalog. View the Online Course Catalog to get started.

The first program, *Legal Aspects for Conducting Clinical Trials*, is comprised of six courses. Individual courses in all programs receive a certificate, and completing the program earns a badge. The second program, *Clinical Trials with Medical Devices*, is comprised of seven courses of which completion of five of the seven courses will earn a badge. Be sure to check out the dashboard features as you build your professional career.

Stay Tuned for More Courses and Programs as We Develop This Free Online Course Catalog!

Webpage: http://regulatory.usc.edu



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Degree Programs

Five Graduate Streams

- DRSC
- **MS Regulatory Science**
- MS Regulatory Management
- MS Management of Drug Development
- MS Medical Product Quality

Certificates

- Food safety
- Regulatory Science
- Early Drug Development
- **Clinical Design and Management**
- Patient and Product Safety

Nancy Smerkanich
DRSc, MS

Assistant Professor
Department of Regulatory and Quality Sciences

piresmer@usc.edu

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Symposiums

- **2015 -** Clinical Trial Hurdles
- **2016 Spring** - Clinical Trial Startup
- **2016 Fall** - Monitoring and Auditing
- **2017 Spring** - Clinical Trials in Special Populations
- **2017 Fall** - Clinical Trials in Era of Emerging Technologies and Treatments
- **2018 Spring** - Regulatory Aspects of Clinical Trial Design
- **2018 Fall** - Pharmacovigilance and Safety Reporting
- **2019 Spring** - Patient-Centered Drug Development and Real World Evidence/Data
- **2019 Summer** - Clinical Trials with Medical Devices
- **2019 Fall** - Legal Aspects of Conducting Clinical Trials
- **2020 Spring** - Quality by Design in Clinical Trials
- **2020 Fall –** Diversity in Clinical Trials in the Time of COVID-19
- **2021 Spring** – Clinical Research Career Pathways (half-day)
- **2021 Spring** – Principles of Global Clinical Research for Medical Devices
- **2021 Fall** - TBD

Symposium recordings are easily accessible for viewing on the SC CTSI's online educational library
https://sc-ctsi.org/training-education/courses?audience=researchProfessionals

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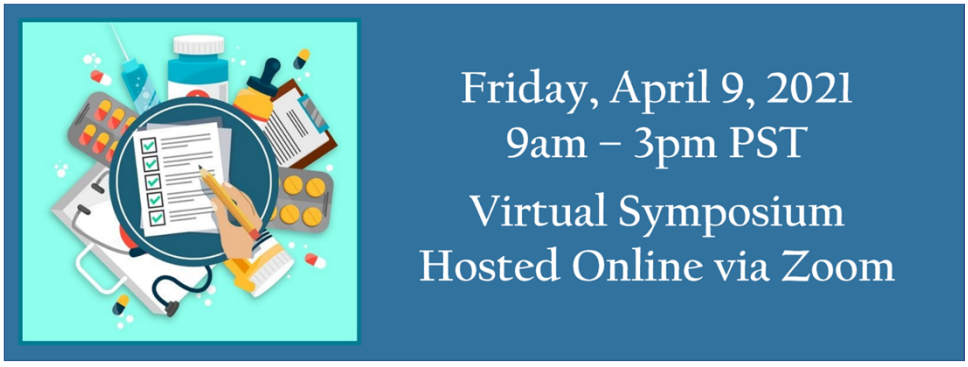
Regulatory Science Virtual Symposium

Principles of Global Clinical Research for Medical Devices



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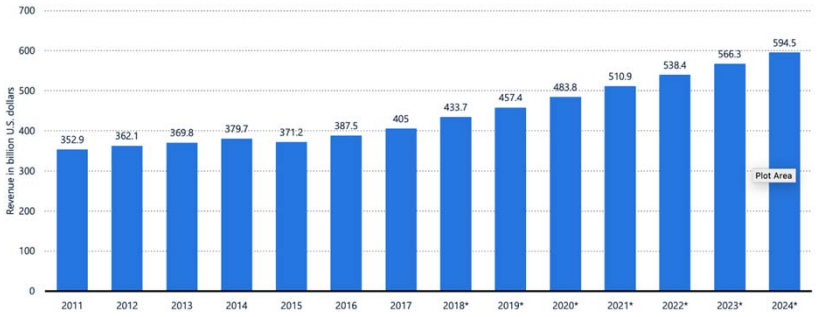
Market Size

Total global medical technology revenue from 2011 to 2024 (in billion U.S. dollars)

Total medtech revenue worldwide 2011-2024



Note: Worldwide; 2011 to 2018
Further information regarding this statistic can be found on page 57.
Source(s): Evaluate; ID 325809

Overview statista

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Device Types

Worldwide Medtech Sales by EvaluateMedTech® Device Area: Top 15 Categories & Total Market (2017 & 2024)

Source: Evaluate, September 2018

Rank	Device Area	WW Sales ($bn) 2017	WW Sales ($bn) 2024	CAGR % Growth	WW Market Share 2017	WW Market Share 2024	WW Market Share Chg. (+/-)	Rank Chg. (+/-)
1.	In Vitro Diagnostics (IVD)	52.6	**79.6**	+6.1%	13.0%	13.4%	+0.4pp	-
2.	Cardiology	46.9	**72.6**	+6.4%	11.6%	12.2%	+0.6pp	-
3.	Diagnostic Imaging	39.5	**51.0**	+3.7%	9.8%	8.6%	-1.2pp	-
4.	Orthopedics	36.5	**47.1**	+3.7%	9.0%	7.9%	-1.1pp	-
5.	Ophthalmics	27.7	**42.2**	+6.2%	6.8%	7.1%	+0.3pp	-
6.	General & Plastic Surgery	22.1	**34.3**	+6.5%	5.5%	5.8%	+0.3pp	-
7.	Endoscopy	18.5	**28.3**	+6.3%	4.6%	4.8%	+0.2pp	+1
8.	Drug Delivery	18.5	**25.3**	+4.6%	4.6%	4.3%	-0.3pp	-1
9.	Dental	13.9	**21.6**	+6.5%	3.4%	3.6%	+0.2pp	-
10.	Diabetic Care	11.7	**19.8**	+7.8%	2.9%	3.3%	+0.4pp	+3
11.	Wound Management	13.0	**17.8**	+4.6%	3.2%	3.0%	-0.2pp	-1
12.	Healthcare IT	11.8	**17.6**	+5.9%	2.9%	3.0%	+0.1pp	-1
13.	Neurology	8.6	**15.8**	+9.1%	2.1%	2.7%	+0.5pp	+3
14.	Nephrology	11.7	**15.6**	+4.2%	2.9%	2.6%	-0.3pp	-2
15.	Ear, Nose & Throat (ENT)	8.9	**13.1**	+5.7%	2.2%	2.2%	+0.0pp	-
	Top 15	342.0	**501.7**	+5.6%	84.4%	84.4%	-0.0pp	
	Other	63.1	**92.9**	+5.7%	15.6%	15.6%	+0.0pp	
	Total WW Medtech Sales	405.0	**594.5**	+5.6%	100.0%	100.0%		

Note: Analysis is based on the top 300 medtech companies. Sales in 2017 based on company reported data. Sales forecasts to 2024 based on a consensus of leading equity analysts' estimates for segmental sales.

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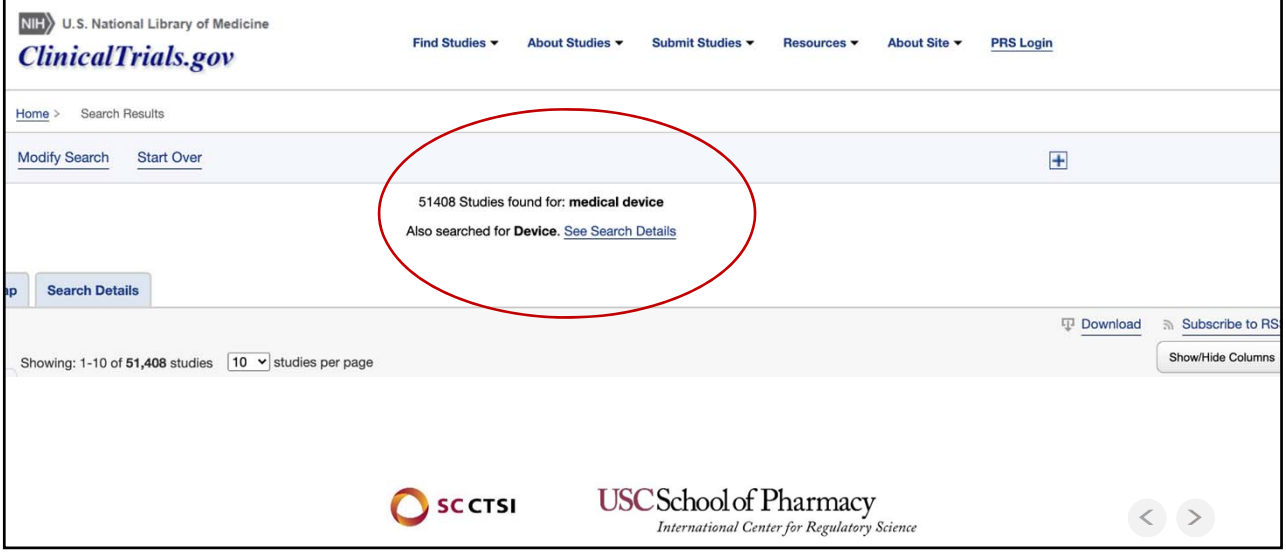
Clinicaltrials.gov: 51,408 studies registered



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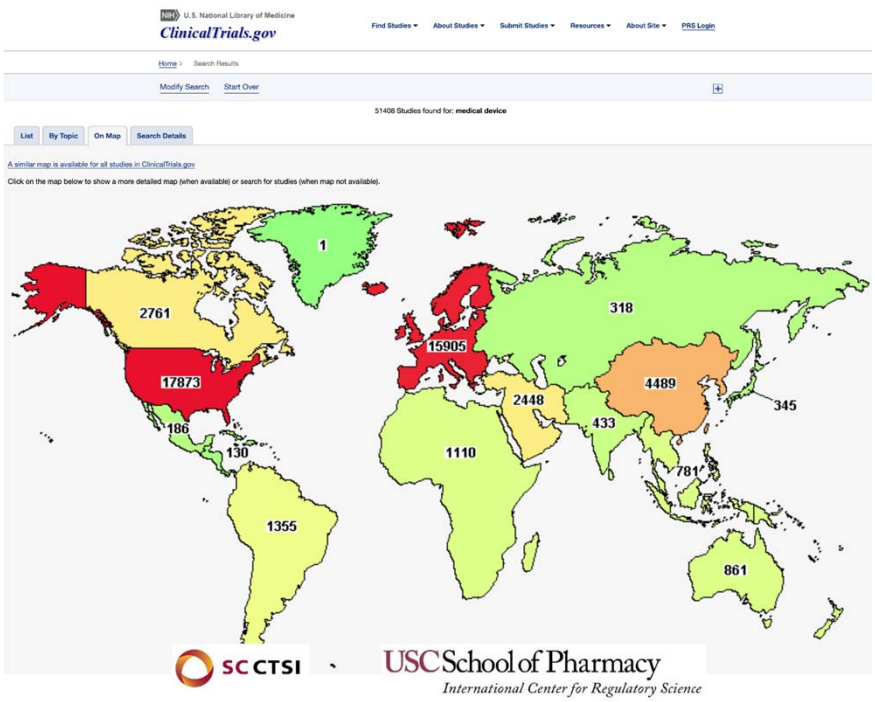

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Agenda

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Presented by the USC School of Pharmacy International Center for Regulatory Science and the Southern California Clinical and Translational Science Institute

This certifies that

Before the end of todays Symposium you will receive a link to take the program evaluation.

Follow this link to the Survey:
Take the Survey

Please complete the program evaluation to receive a certificate of completion by Friday, April 23, 2021.

Eunjoo Pacifici, PharmD, PhD
Director
International Center for Regulatory Science

Thomas A. Buchanan, MD
Director
Southern California Clinical and Translational Science Institute

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Clinical Investigation: value and key aspects of the IMDRF guidance document

Maria E. Donawa, M.D.
President, Donawa Lifescience

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Learning objectives (and topics)

Understand	key aspects of the evolution of good clinical practice (GCP) concepts for medical devices
Become	familiar with general aspects of the history of IMDRF and its clinical documents
Recognize	link between clinical investigation, clinical evidence, and clinical evaluation
Understand	value of the IMDRF clinical investigation guidance and its links to standards and regulations, using Europe and the US as examples

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2

Evolution of GCP concepts for medical devices

Pharmaceutical GCPs			
460BC	Oath of Hippocrates	1996	ICH-GCP guidelines issued
1930s	US Food, Drug and Cosmetic Act	1997	FDA endorsement of GCP ICH guidelines
1947	Nuremberg Code	1998	Japan GCP*
1948	Declaration of Human Rights	1998	Singapore GCP
1962	Kefauver-Harris Amendment	1999	Malaysian GCP
1964	Declaration of Helsinki	2000	Thailand
1979	Belmont Report	2001	Indonesia
1982	International Guidelines for Biomedical Research Involving Human Subjects	2001	European Directive on GCPs

Information on Asia-Pacific (this and next slide)

Vijayananthan A. The importance of Good Clinical Practice guidelines and its role in clinical trials. *Biomed Imaging Interv J.* 2008 Jan-Mar; 4(1): e5.

*Inoue H. Good Clinical Practice in Japan: Current Status and Future Perspectives. *Drug Information Journal*, Vol 32. 1998, p 1213S-1215S

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3

Evolution of GCP concepts for medical devices

Medical device regulations and requirements	
1976	US Medical Device Amendments
1990s	European Directives for medical devices

European GCP medical devices standard	
1993	EN 540:1993 Clinical investigation of medical devices for human subjects (only 10 pages!)

International GCP medical devices standards	
2003	ISO 14155-1:2003 Clinical investigation of medical devices for human subjects - Part 1: General requirements ISO 14155-2 Clinical investigation of medical devices for human subjects - Part 2: Clinical investigation plans
2011	ISO 14155:2011 Clinical investigation of medical devices for human subjects — Good clinical practice
2020	ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice

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4

Evolution of GCP concepts for medical devices

Human Subject Protection; Acceptance of Data From Clinical Investigations for Medical Devices

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

§ 812.28 Acceptance of data from clinical investigations conducted outside the United States

Sec 812.28(a)(1)
Good clinical practice (GCP) is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical investigations in a way that provides assurance that the data and results are credible and accurate and that the rights, safety, and well-being of subjects are protected. GCP includes review and approval (or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating an investigation, continuing review of an ongoing investigation by an IEC, and obtaining and documenting the freely given informed consent of the subject (or a subject's legally authorized representative, if the subject is unable to provide informed consent) before initiating an investigation.

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Evolution of GCP concepts for medical devices

ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice

Clause 4 Summary of good clinical practice (GCP principles)

a) Clinical investigations shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (see Reference [7]), and that are consistent with this document.

b) Before a clinical investigation is initiated, foreseeable risks and inconveniences shall be weighed against the anticipated benefit for the individual subject and society. A clinical investigation shall be initiated and continued only if the anticipated benefits justify the risk.

c) The rights, safety, and well-being of human subjects are the most important considerations and prevail over interests of science and society.

d) The available non-clinical and clinical information on the investigational device shall be adequate to support the proposed clinical investigation.

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Evolution of GCP concepts for medical devices

e) Clinical investigations shall be scientifically sound and described in a clearly detailed CIP.

f) A clinical investigation shall be conducted in compliance with the CIP that has received prior ethics committee approval/favourable opinion and, where applicable, approval/non-objection of regulatory authorities.

g) The medical care given to, and medical decisions made on behalf of subjects shall always be the responsibility of a qualified healthcare professional.

h) Each individual involved in designing, conducting, recording, and reporting a clinical investigation shall be qualified by education, training, and experience to perform his or her respective task(s).

i) Freely given informed consent shall be obtained from every subject prior to the participation in the clinical investigation.

NOTE 1 Some exceptions can exist (see 5.8.3).

Evolution of GCP concepts for medical devices

j) All clinical investigation related information shall be recorded, handled, and securely stored in a way that allows its accurate reporting, interpretation, monitoring, auditing, and verification.

k) The confidentiality of records that could identify subjects shall be protected, respecting the privacy and confidentiality rules.

l) Investigational devices shall be designed, manufactured, handled, and stored in accordance with the essential principles (see Reference [7]). They shall be used in accordance with the approved CIP, the IB and manufacturer's instructions for use.

NOTE 2 Essential principles can be further outlined in national regulations.

m) Systems with procedures that ensure the quality of every aspect of the clinical investigation shall be implemented.

History of IMDRF and its clinical documents

During the late 1980s and the dawn of the 1990s, the need for harmonizing the globally disparate systems for regulating medical devices was discussed intensely and at many important conferences. Each country and region had its own system or no system!

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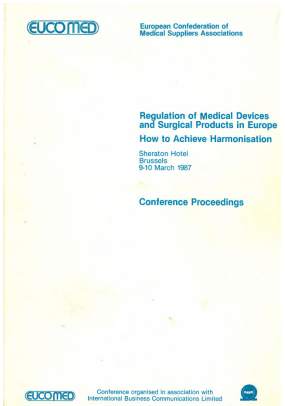
History of IMDRF and its clinical documents

HIMA (early version of AdvaMed) International Trade Conference on EC 1992: Status of Developments Affecting the Healthcare Technology Industry



EUCOMED (together with EDMA, became MedTech Europe

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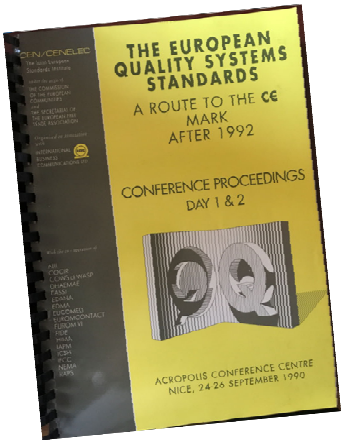
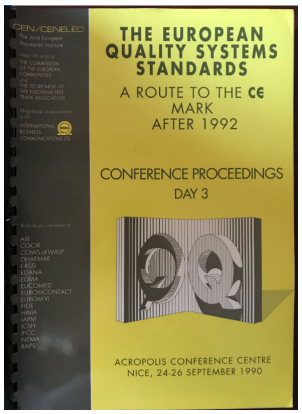
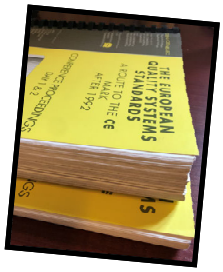
History of IMDRF and its clinical documents







Forward to Proceedings
"Three years ago, CEN like CENELEC, was unknown to the medical device sector. The 700 experts present at the conference demonstrate that this is no longer the case."

1990 Conference
CEN / CENELEC, Commission of the European Commission, Secretariat of European Free Trade Association, broad participation, e.g., US FDA, European regulators, various industry trade associations, Notified Bodies, others

History of IMDRF and its clinical documents

And then there was a global medical device conference in Nice, France in the Fall of 1992!

History of IMDRF and its clinical documents

Landmark meeting!

- Birth of the Global Harmonization Task Force (GHTF)
- Founding members were representatives from industry and regulators from EU, US, Canada, Japan and Australia
- Critical beginning of work on global harmonization of medical device regulatory principles
- Gordon Higson was a key figure in this effort as explained in next slide

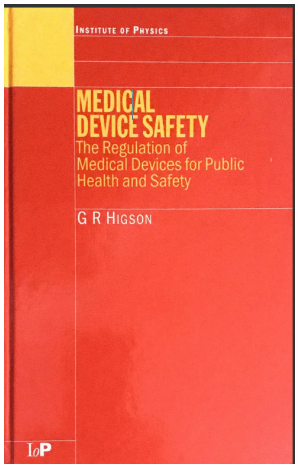
History of IMDRF and its clinical documents

Just a word about Gordon Higson, one of the persons responsible for the creation of GHTF

In 1992, Gordon was Chairman, Medical Technology Consultants Europe Ltd, but previously was Director of UK Department of Health and Social Security (DHSS), responsible for development of UK approach to medical device regulation (I met Gordon during my time with FDA in the 1980s).

He was extremely passionate regarding the importance of harmonizing medical device regulations and penned a very well written and informative book (at the right), Medical Device Safety, The Regulation of Medical Devices for Public Health and Safety, published in 2002.

Gordon died suddenly in 2001, just after approving the final proofs of the book.



History of IMDRF and its clinical documents

- GHTF active operation from January 1993 through late 2011
- Purpose was to encourage convergence of global medical device regulatory practices
- Method was to publish and disseminate harmonized guidance documents on basic regulatory practices
- Study Groups were set up:
  - Study Group 1 - Premarket Evaluation
  - Study Group 2 - Post-Market Surveillance/Vigilance
  - Study Group 3 - Quality Systems
  - Study Group 4 - Auditing
  - Study Group 5 - Clinical Safety/Performance

History of IMDRF and its clinical documents

GHTF Study Group 5 - Clinical Safety/Performance		
May 2007	Clinical Evidence – Key Definitions and Concepts	SG5/N1R8:2007
May 2007	Clinical Evaluation	SG5/N2R:2007
12 Feb 2010	Clinical Investigations	GHTF/SG5/N3:2010
18 Feb 2010	Post-Market Clinical Follow-Up Studies	GHTF/SG5/N4:2010
10 Aug 2012	Reportable Events During Pre-Market Clinical Investigations	GHTF/SG5/N5:2012

Note: IVD clinical evidence documents were also developed

History of IMDRF and its clinical documents

- Documents developed by Working Groups
- Medical Device Clinical Evaluation (www.imdrf.org/workitems/wi-mdce.asp)
- Working Group Chair: Dr. Yinghui Liu, China

  Membership: Regulatory and stakeholder membership

  Listed stakeholders
  Global Diagnostic Imaging, Healthcare IT & Radiation Therapy Trade Association (DITTA): FUJIFILM Corp, Elekta, Philips

  Global Medical Technology Alliance (GMTA): Alcon, Johnson & Johnson Medical, Medtronic

History of IMDRF and its clinical documents

- Created in February 2011; formally launched in October 2011
- *Forum of voluntary medical device regulators from around the world who have come together to build on the strong foundational work of the Global Harmonization Task Force on Medical Devices (GHTF), and to accelerate international medical device regulatory harmonization and convergence*.
- www.imdrf.org/index.asp - everything you need to know is here

History of IMDRF and its clinical documents

IMDRF MDCE Documents		
10 Oct 2019	Clinical Evidence – Key Definitions and Concepts	IMDRF MDCE WG/N55FINAL:2019
10 Oct 2019	Clinical Evaluation	IMDRF MDCE WG/N56FINAL:2019
10 Oct 2019	Clinical Investigations	IMDRF MDCE WG/N57FINAL:2019

Link between clinical investigation, clinical evidence, and clinical evaluation

Clinical evidence	The clinical data and its clinical evaluation pertaining to a medical device.
Clinical data	Safety, clinical performance, and/or effectiveness information that is generated from the clinical use of a medical device.
Clinical evaluation	A set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance, and/or effectiveness of the medical device when used as intended by the manufacturer.

Link between clinical investigation, clinical evidence, and clinical evaluation

Sources of clinical data from MDR Article 48 "clinical data" (see MDR for complete text)

- Clinical investigation of device concerned
- Clinical investigation of equivalent device
- Reports in peer reviewed scientific literature on other clinical experience of either device concerned or equivalent device
- Clinically relevant information from post-market surveillance, in particular, post-market clinical follow-up

Value of IMDRF clinical investigation guidance

IMDRF/ MDCE WG/N57FINAL:2019 (formerly GHTF/SG5/N3:2010)

IMDRF International Medical Device Regulators Forum

FINAL DOCUMENT

International Medical Device Regulators Forum

Title: Clinical Investigation

Authoring Group: Medical Device Clinical Evaluation Working Group

Date: 10 October 2019

Elena M. Astapenko, IMDRF Chair

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Contents

Value of IMDRF clinical investigation guidance

Introduction	Critical elements (e.g., what is a clinical investigation, what is its objective, and how is it conducted, referring to ISO 14155)
Scope	(1) when a clinical investigation should be undertaken to demonstrate compliance with relevant Essential Principles and (2) general principles of medical device clinical investigations
References	IMDRF/GHTF final documents, international standards, and other references
Definitions	16 definitions provided
General Principles When Considering the Need for a Clinical Investigation	Concise and helpful guidance on how to determine need for clinical investigation, including helpful flow chart
General Principles of Clinical Investigation Design	Provides key considerations on study design, including factors related to extent of data requirements, considerations for study protocols, reference to ISO 14155 re GCPs, and need to document study outcome in a final study report
Ethical Considerations for Clinical Investigations	Describes essential elements related to ethical considerations

Value of IMDRF clinical investigation guidance

- Provides the essential elements regarding medical device clinical investigation requirements upon which to build an approach to local regulation
- Reflects broad agreement among parties participating in the development of the document
- Clear evidence of acceptance by regulatory regimes
  - EU Medical Device Regulation (2017/745)
  - US FDA regulations (see preambles of final rules)
  - Others…

Value of IMDRF clinical investigation guidance

MDR Recital #5 (preamble statements)

*To the extent possible, guidance developed for medical devices at international level, in particular in the context of the **Global Harmonization Task Force (GHTF)** and its follow-up initiative, the **International Medical Devices Regulators Forum (IMDRF)**, should be taken into account to promote the global convergence of regulations which contributes to a high level of safety protection worldwide, and to facilitate trade, in particular in the provisions on Unique Device Identification, general safety and performance requirements, technical documentation, classification rules, conformity assessment procedures and clinical investigations.*

Value of IMDRF clinical investigation guidance

US 21 CFR Parts 807, 812 and 814
FDA Final Rule, Human Subject Protection; Acceptance of Data From Clinical Investigations for Medical Devices (Federal Register, Vol. 83, No. 35, 21 February 2018)

Section IV, Comments on the Proposed Rule, Section A, International Harmonization, states "… *FDA plays a key role in forums such as the International Medical Device Regulators Forum (IMDRF) where global medical device good clinical practice was discussed during the IMDRF meeting in Florianopolis, Brazil, in September 2016. Additionally, FDA continues to be directly involved in good clinical practice standard development, including those of the International Organization for Standardization (ISO) and the International Conference on Harmonisation (ICH).*"

Key take-aways

Medical device GCPs have a long history of evolution from basic concepts to detailed requirements for pharmaceutical trials, and finally development of specific GCPs for medical device clinical investigations

Significant efforts on medical device harmonization led to the founding of the GHTF, operating effectively for 18 years, with regulators and industry contributing to development of critical harmonization guidance documents, eventually leading to the birth of IMDRF

Clinical evidence consists of the clinical data and its clinical evaluation pertaining to a medical device

IMDRF clinical investigation guidance provides the key elements upon which to build regulatory requirements regarding the need for and conduct of medical device clinical investigations

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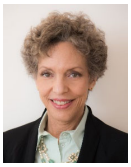
Donawa Lifescience



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GCP – ISO 14155:2020

9 April 2020

Danielle Giroud
CEO MD-CLINICALS and WMDO

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GCP-ISO 14155

- Key learning objectives:
  - GCP aspects for medical devices – how they differ from pharmaceuticals
  - Requirements of ISO 14155 regarding demonstration of benefit-risk profiles of medical devices
  - Determine different study phases in a medical device global clinical strategy.

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ISO 14155:2020 – Scope

This International Standard addresses good clinical practice for the design, conduct, recording and reporting of pre-market clinical investigations carried out in human subjects to assess the **clinical performance** or **effectiveness** and **safety** of medical devices

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ISO 14155:2020 – Scope

'*The principles set forth in this standard also apply to all other clinical investigations and should be followed as far as relevant, considering the nature of the clinical investigation.*

Annex I (informative) clinical development stages

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ISO 14155:2020 – Applicability

Annex I: Clinical Development Stages

Regulatory status	PRE MARKET		POST MARKET	
Clinical development stage	Pilot stage (I.3.1)	Pivotal stage (I.3.2)	Post market stage (I.3.3)	
Type of design	Exploratory or confirmatory (I.4.1)	Confirmatory (I.4.2)		Observational (I.4.3)
Descriptors of clinical investigations	First in human clinical investigation (I.5.1) Early feasibility clinical investigation (I.5.2) Traditional feasibility clinical investigation (I.5.3)	Pivotal clinical investigation (I.5.4)	Post market clinical investigation (I.2.2)	Registry (I.5.5) Post market clinical investigation (I.2.2)
Burden to subject	Interventional (I.6.1)		Interventional (I.6.1)	Non-Interventional (I.6.2))

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ISO 14155:2020 – Applicability

Annex I Section 7
Suggested waivers

	Post market confirmatory (interventional)	Post market observational (non-interventional)
Device accountability	When market approved devices are used within their intended use	Where commercial products are used
Labelling	Specific for clinical investigations	Specific for clinical investigations
Investigator brochure	When sufficient information is available for the use of the MD within its intended use	Where sufficient commercial information is available
Reporting to regulatory authorities	Depending on national regulations	Reporting to national authorities unless other national requirements apply

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ISO 14155:2020 – Applicability

Annex I Section 7
Suggested waivers

	Post market confirmatory (interventional)	Post market observational (non-interventional)
Informed consent	Not waived	As per EC requirements except data protection consent
CV members of investigation team	Not waived	Waived

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ISO 14155:2020 – Scope

Scope more defined


IMDRF/SaMD WG/N41FINAL:2017

IMDRF International Medical Device Regulators Forum

Final Document

Title: Software as a Medical Device (SaMD): Clinical Evaluation
Authoring Group: Software as a Medical Device Working Group

Date: 21 September 2017

J. Patrick Stewart, IMDRF Chair

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NOTE 1 Users of this document will need to consider whether other standards and/or national requirements also apply to the investigational device(s) under consideration or the clinical investigation. If differences in requirements exist, the most stringent will apply.

NOTE 2 For Software as a Medical Device (SaMD), demonstration of the analytical validity (the SaMD's output is accurate for a given input), and where appropriate, the scientific validity (the SaMD's output is associated to the intended clinical condition/physiological state), and clinical performance (the SaMD's output yields a clinically meaningful association to the target use) of the SaMD the requirements of this standard apply as far as relevant (see Reference [5]). Justifications for exemptions of this standard can consider the uniqueness of indirect contact between subjects and the SaMD.

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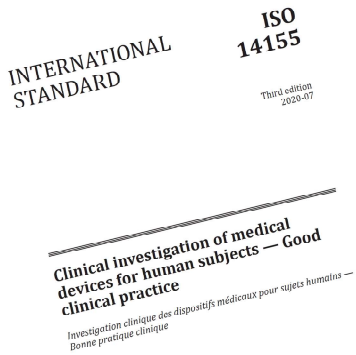
ISO 14155:2020 – Scope

This document does not apply to in vitro diagnostic medical devices. However, there may be situations, dependent on the device and national or regional requirements, where users of this document might consider whether specific sections and/or requirements of this document could be applicable.



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ISO 14155:2020 – Summary of GCP

Summary of GCP

Align with ICH GCP (R2) adapted to medical devices

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ISO 14155:2020 – General

Recording in public data base

- A description of the clinical investigation shall be registered in a public accessible data base prior to first subject enrolment.
- The contents of the registration shall be updated throughout the conduct of the clinical investigation
- Inform the subject about this publication in the ICF

Accordance with Declaration of Helsinki

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ISO 14155:2020 – General

Medical Expertise

- The sponsor shall have access to the medical expertise relevant to the clinical investigation.

Note: medical expertise is provided by a person qualified by education, training and experience, who will be readily available to advise on the clinical investigation related medical questions or problems. If necessary, outside consultant(s) may be available for this purpose

Align with ICH-GCP

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ISO 14155:2020 – Ethics – Informed Consent

Additional element

- Inform subject that data may be exported to foreign countries.
- Inform subjects about what will be done with sample taken and stored for future use.

Accordance with data protection regulations

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ISO 14155:2020 – Ethics – Informed Consent

Additional element

- Add a name of a contact person in the informed consent in addition to the GP that can be contacted in case subject is not responding.

Requested by EU competent authorities, avoid easy drop out considerations.

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ISO 14155:2020 – Risk Management

Risks related to the use of the investigational medical device

Risks related to the conduct of the clinical investigation

RA to IB, IFU, CIP, ICF

CIP and Mon plan

The sponsor shall pre-define quality tolerance limits or establish threshold limits, and trigger a risk assessment to determine if actions are needed to improve compliance as soon as threshold are reached or exceeded

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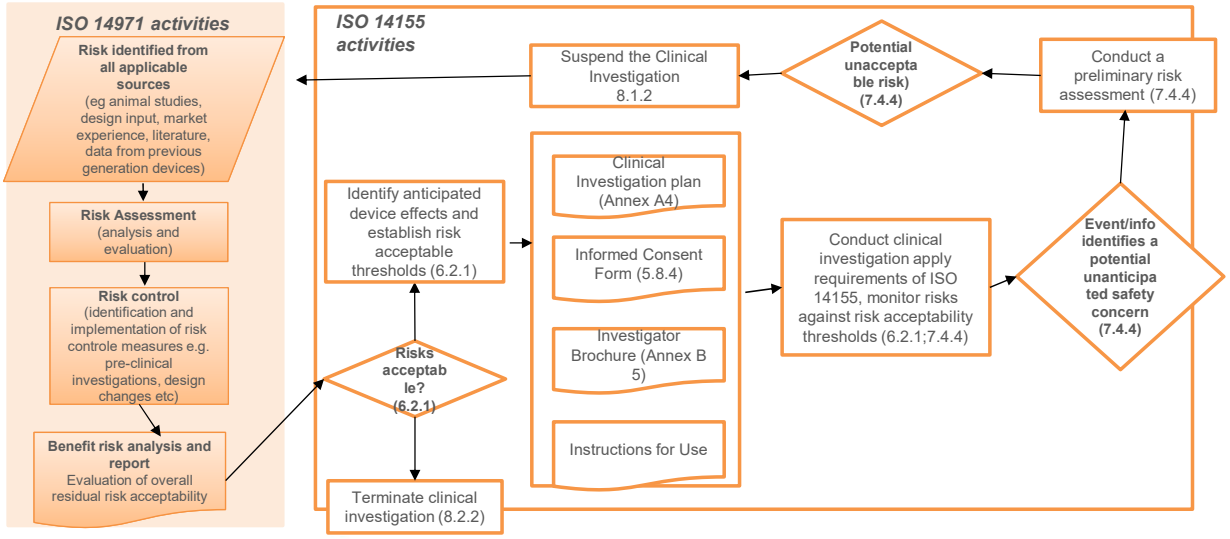
ISO 14155:2020 – Risk Management – Annex H



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ISO 14155:2020 – Risk Management

Risk based monitoring

- Onsite vs centralised monitoring
- Onsite requirements in case of centralised monitoring
- Additional emphasis on training of site personnel
- Pre-define in CIP and monitoring plan
  - Risk related to the conduct of the clinical investigation
  - Thresholds and escalation methods in case the thresholds are reached

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ISO 14155:2020 – Risk Management

Risk based monitoring

- Evaluate project risks
- Establish mitigation – monitoring etc
- Pre-define thresholds - escalation
- Monitor and report/escalation
- Suspend/Implement CAPAs
- Verify

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ISO 14155:2020 – Quality Management

Gap analysis with ISO 13485/US QSR

- Provide guidance on readiness of the investigational device for human use
- Documentation of good manufacturing processes
- Requirements for written procedure to handle non-conforming products
- Management of product related CAPA
- Need for updating IB with design changes if any

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ISO 14155:2020 – Quality Management

Gap analysis with ISO 13485/US QSR

- Provisions for explant retrieval and retrieval analysis
- Details on what to do with 'unused investigational devices' at the end of a clinical investigation.
- Integrate clinical quality system into overall company QS or keep separate

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ISO 14155:2020 – Annex A – Clinical Investigation Plan – What is new ?

Device description	Reference needed to IB and IFU for further information
Justification of design	Description of clinical development stage
Objectives/hypothesis	○ Define claims – as a basis for objectives and eligibility criteria ○ Primary and secondary objectives – including where applicable, superiority, inferiority, equivalence. ○ Scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits (if applicable)

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ISO 14155:2020 – Annex A – Clinical Investigation Plan – What is new ?

Design - general	○ Absence of controls to be justified ○ Composite endpoints – rational for selection and measurement ○ Primary endpoint is important and clinical relevant ○ Investigation sites number, location and environment ○ Definition of completionof the clinical investigation

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ISO 14155:2020 – Annex A – Clinical Investigation Plan – What is new ?

Design - subjects	○ Criteria for withdrawal or lost to follow up - when/how to withdraw or stop the use of the device - Document efforts to trace subjects - Replacement of subjects (if applicable) ○ Distribution of enrolment among sites ○ Relationship to target population ○ Information on vulnerable, pregnant and breastfeeding population if needed

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ISO 14155:2020 – Annex A – Clinical Investigation Plan – What is new ?

Design - Procedures	○ Deviation from normal practice of procedures in the clinical investigation ○ Methods for addressing factors that can compromise the outcome or interpretation of results ○ Address Follow up for subjects after study closure ○ Address final disposition or potential future use of samples obtained from subjects (if applicable)

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ISO 14155:2020 – Annex A – Clinical Investigation Plan – What is new ?

Statistical considerations	○ Identify analysis population (ITT, PP, AT) and procedures to take into account all data. ○ Descriptive statistics for baseline data, treatments, safety data and primary and secondary endpoints ○ Analytical procedures including methods of precision (SD) ○ The significance level and power of the primary endpoint(s) and overall statistical testing strategy

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ISO 14155:2020 – Annex A – Clinical Investigation Plan – What is new ?

Statistical considerations	○ Sample size calculation and justification taking into account - Expected drop out rates ○ and if applicable… - All relevant clinical data on outcome variable and effect size - Assumptions of expected outcomes accross treatment groups - Adjustments due to any planned interim analyses - Detected effect size and non-inferiority margin (smaller than the effect size and justified with referene to the effect of the comparator) - Randomization ratio

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ISO 14155:2020 – Annex A – Clinical Investigation Plan – What is new ?

Statistical considerations	○ Describe all stats parameters and methos used to calculate sample size or non-inferiority margin. ○ Provide justification for sample size for observational or exploratory studies ○ Description of learning curve (number of use per user) ○ Management of bias and plan for success of method used ○ Management of confounding factors (adjustments, stratification etc)

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ISO 14155:2020 – Annex A – Clinical Investigation Plan – What is new ?

Statistical considerations	○ Procedures for multiplicity control and adjustment of error probabilities ○ Specification of subgroups and if response is expected to be different in the groups ○ Exploratory analysis and sensitivity analysis ○ Procedure for deviations from initial SAP ○ Provisions for balance or handling of inbalance of numbers of subjects accross the different sites ○ Strategy for pooling data if needed

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ISO 14155:2020 – Annex A – Clinical Investigation Plan – What is new ?

Data Management	○ Identification of the method of data collection ○ Procedures for all activities and tracking thereof ○ Procedures for verification, validation and securing EDC systems ○ Procedures to protect subject privacy ○ Methods for data base locking and storage/archiving
Device Accountability	○ Procedures and particular materials and instructions for safe return of investigational devices including and especially those that may be potentially biohazardous
Statements of compliance	○ Statement addressing the financing of the clinical investigation including description of the agreement between sponsor and investigation site(s) and/or investigator. [reference to the agreement]

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ISO 14155:2020 – Annex A – Clinical Investigation Plan – What is new ?

AE, ADE and DD	○ List of non-reportable Aes if applicable and rational for non-reportability ○ Reporting of AEs should include not only relationship to the investigational device but also to the procedure involved
Vulnerable population	○ Description of screening process to identify and protect the vulnerable population
Suspension or premature termination	○ Requirements not only for subject follow up but also for continued care

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ISO 14155:2020 – Annex A – Clinical Investigation Plan – What is new ?

Publication	○ Statement about registration in a publicly accessible data base ○ Statement that results will be made publicly available ○ Statement about conditions and timeframes of publication of study results including role of sponsor and criteria for authorship

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ISO 14155:2020 – Overview of Annexes

Normative Annexes

- Annex A: CIP
- Annex B: IB
- Annex D: Clinical investigation report

Informative Annexes

- Annex C: CRF
- Annex E: Essential documents
- Annex F: Adverse events/Device deficiency
- Annex G: Ethics Committee guidance
- Annex H: Risk Management
- Annex I: Clinical development stages
- Annex J: Audit

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ISO 14155:2020 – Quality Management

Implementation

- Publication July 2020
- Immediately implementable
- Harmonization to MDR?

ISO 14155:2020 Is considered state of the art –
use for any study aiming registration under MDR!

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From Clinical Data to Clinical Evidence

Cheryl Hergert, MPH

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Agenda

- Defining Evidence
- The need for evidence
- Types of evidence
- Validating Evidence
- Case studies

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Definition

- **Evidence**: something that furnishes proof; specifically, something legally submitted to a tribunal to ascertain the truth of a matter. (Merriam-Webster Dictionary)
- **Clinical evidence**: the clinical data and the clinical evaluation report pertaining to a medical device. (IMDRF)

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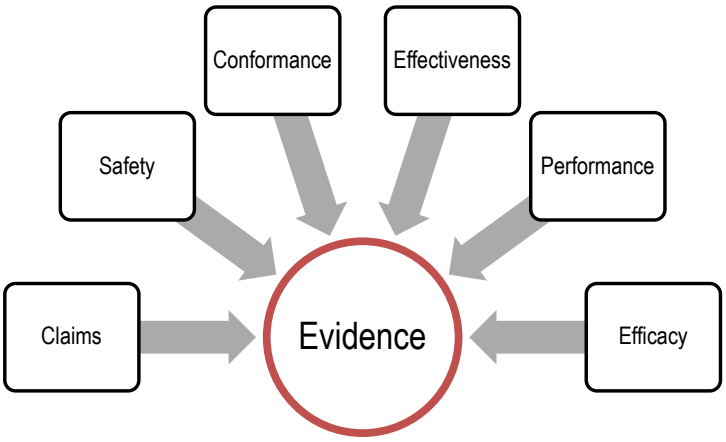
Evidence is the persuasive argument



Evidence guides **regulatory decision making** which leads to **action**.

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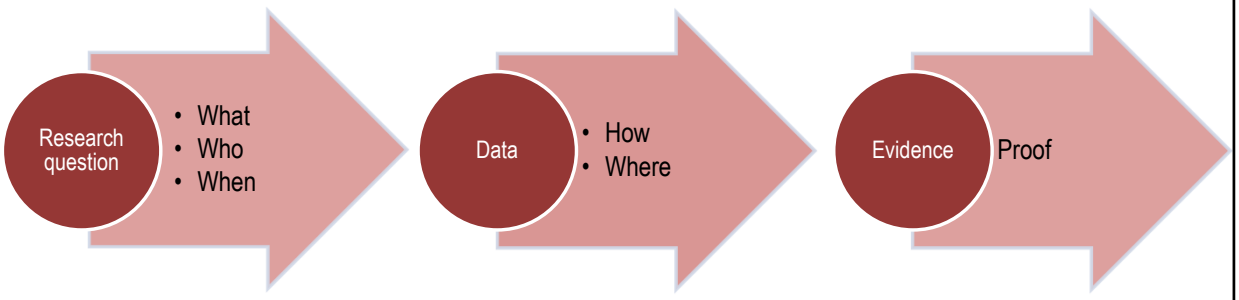
Driver: Research question



The research question determines **study design** which provides the **evidence**.

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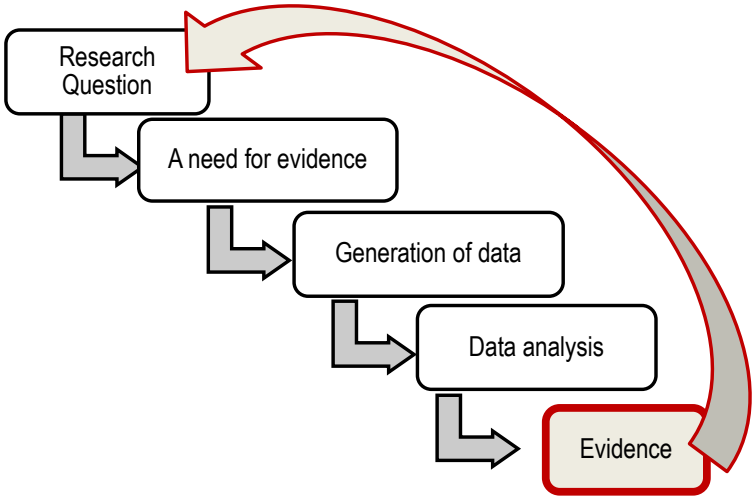
Digging deeper: generating data



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Research question

Leading questions:

- Why is evidence needed?
  - Proof of concept
  - Feasibility
  - Market approval
  - Post Market assessments
- What do we know?
- What don't we know?
- What do we need to know?

Research question provides the framework for:
-Study design
-Type of data
-Analysis plan

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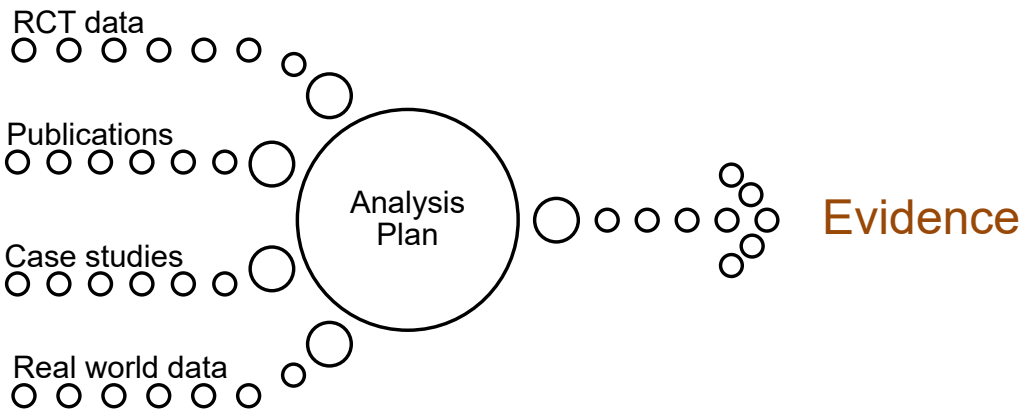
Finding data



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Research designs that generate evidence

Randomized controlled trials (RCT)
- Within subject treatment group
- Standard of care treatment group
- Sham treatment group
- Historical data (matched*)
- Routine clinical data (RCD) (matched*)

(*Propensity score matching used to match individuals of different treatment groups at baseline.)

Alternative research trial designs:
- Pragmatic trial
- Observational study
- Registries
- Meta-analysis of published results
- Case studies

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RCT issues

When might the gold standard not be the right design:
- Randomizing to invasive surgeries.
  - Ethical issues with sham surgery
  - Limited ability to blind subject and investigator
  - Ineffective noninvasive comparator
  - Standard of care treatment less effective than investigative treatment
- Cost and timeliness prohibitive.
- Right design for the research question?
  - Effectiveness in real world practice.
  - The need to generalize the evidence.

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Real world data (RWD)

- Sources include:
  - Electronic health record database
  - Patient reported outcomes
  - Patient chart reviews
  - Registries
  - Wearable device data
  - Social media

- Real world data (RWD) can become real world evidence (RWE).
- RWE is generalizable.

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Pause: Let's review terms

- **Real world data (RWD):** data relating to patient health status and/or delivery of health care routinely collected from a variety of sources. (FDA)
- **Real world evidence (RWE):** the clinical evidence regarding the usage, and potential benefits or risks, of a medical device product derived from analysis of RWD. (FDA)
- **Routine clinical data (RCD):** data obtained from ongoing data collection systems associated with the health and social services. (Segen's Medical Dictionary)

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Pause: Let's review terms

- **Pragmatic design:** evaluates the effectiveness of interventions in real-life routine practice conditions; produces results that can be generalized and applied in routine practice settings. (Patsopoulos)
- **Observational design:** a study that does not involve any intervention (experimental or otherwise) on the part of the investigator. The investigators observe without intervening other than to record, classify, count, and analyze results. (FDA)
- **Propensity score:** an efficient remedy to obtaining unbiased estimates of treatment effectiveness by adjusting or balancing treatment group differences based on a single composite characteristic. (International Encyclopedia of Education)

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Quality of evidence

The quality of evidence depends on the quality of the data.

- Missing data
- Incorrect data
- Subject attrition
- Wrong data type
- Data with weak validity
  - Does it address bias?
  - Is it generalizable?

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Validity of evidence

- **Internal validation:** ability to attribute any difference between treatment groups to the intervention. Effected by bias and random error.
- **External validation:** extent to which the results can be generalized to other clinical situations, such as routine care.

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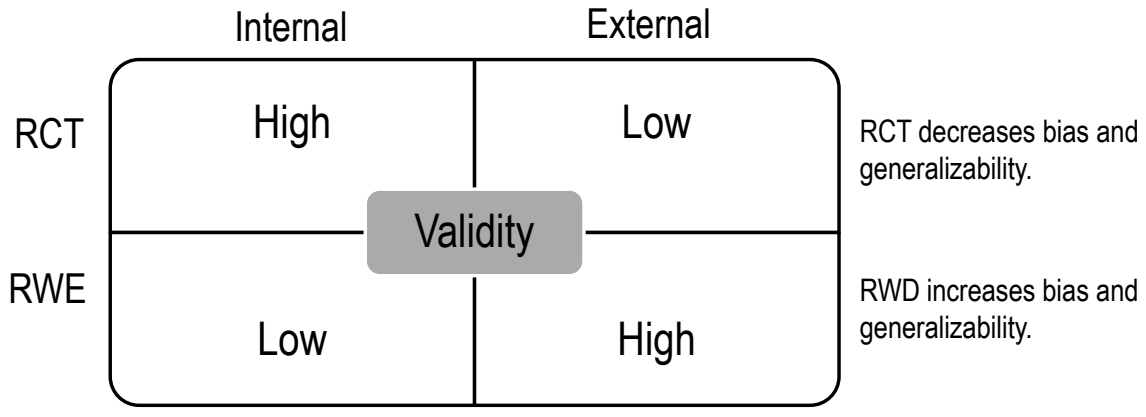
Validity of evidence



RCT decreases bias and generalizability.

RWD increases bias and generalizability.

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Internal Validity

Minimizing bias increases internal validity

Selection bias	Performance bias	Detection bias	Attrition bias
• Randomization • Stratification • Blind to randomization algorithm	• Blind to treatment • Blind to treatment advantage	• A priori statistical plan • Monitoring • Appropriate analyses • Interpretation of results	• Intent to treat (ITT) analysis • Per protocol (PP) analysis

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Internal Validity

Reduction of random error increases internal validity.

Caused by
- Testing variability
- Sample size

Minimized by
- Core lab
- Clinic staff training
  - Example: 6 Minute Walk variability
- Conservative sample size
  - Power calculations
  - Larger is better

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Case study: Mitraclip (Tarricone, 2016)

- Percutaneous implant for mitral regurgitation.
- Successful RCT assessed Mitraclip to conventional mitral valve surgery.
- Implantable device launched in 2008.
- Post market retrospective analysis of clinical records (2016). RWD
  - Mitraclip + SOC vs SOC alone.
    - Treatment 1: patients who received Mitraclip.
    - Treatment 2: patients eligible for Mitraclip but who did not receive it.
      - Propensity score was used to significantly reduce selection bias.
  - Submitted for publication - used as opportunity to inform clinical field.
    - Publication was rejection.
    - Due to perceived inherent differences between an RCT and real-world trial designs.

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Case study: Senhance Surgical System (510k K171120 , 2017)

- Robotic device intended to assist in laparoscopic colorectal surgery and gynecological surgery.
- Prospective non-randomized clinical trial.
- Results from surgeries with Senhance Surgical System were compared to RWD
  - Published literature utilizing medical records,
  - Retrospective review of medical records (EHR, EMR or chart review).
- **RWE was the primary source of clinical evidence.**
- Successful clearance of New Robotically Assisted Surgical Device.

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Summary Points to Consider

- Research question will determine study design/data which provides the evidence.
- Quality of data impacts quality of evidence.
- Internal / external validity impacts the validity of the evidence.
- RWE is different and not inferior to RCT evidence.
- RCTs aim to show a technology works; RW studies aim to show if a technology works in a clinical setting.

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Questions?

Thank you

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References

1. Merriam-Webster Dictionary.
2. International Medical Device Regulators Forum Glossary.
3. FDA, 2017. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices - Guidance for Industry and Food and Drug Administration Staff.
4. Segen's Medical Dictionary.
5. International Encyclopedia of Education.
6. Patsopoulos, 2011. A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci.* 13(2): 217–224.
7. Tarricone, R., 2016. What type of clinical evidence is needed to assess medical devices? *Eur Respir Rev.* 25: 259–265.
8. FDA, 2021. Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions.
9. Akonbeng, A., 2008. Assessing the validity of clinical trials. *Journal of Pediatric Gastroenterology and Nutrition*. 47: 277-282.

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Developing Clinical Evaluations

Evangeline Loh, PhD, RAC (US, EU)
Global Regulatory Manager, Emergo by UL

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Learning Objectives

- What is clinical data
- What is clinical evaluation
- How is clinical evaluation performed
- How is clinical evaluation documented
- Why is clinical evaluation important

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Clinical Evaluation
Definitions Clinical Data

- 'Clinical data' means the **safety**, **clinical performance and/or effectiveness information** that is generated from the **clinical use of a device**.

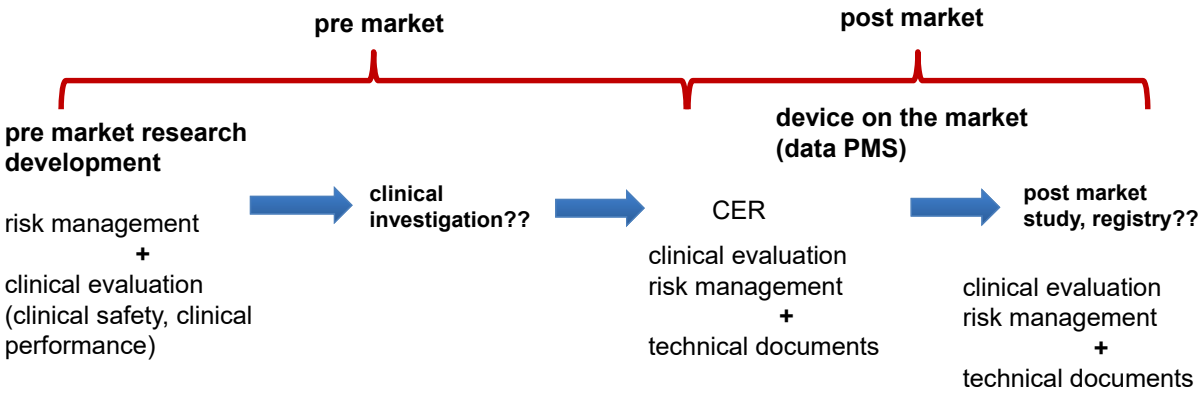
- Clinical data are sourced from (Section 6.0):
  - scientific literature of the device in question (or comparable device) (6.1);
  - clinical experience of the device in question (or comparable device) (6.2);
  - clinical investigation(s) of the device in question (or comparable device) (6.3);
  - "clinical experience and literature reports of the safety, clinical performance and/or effectiveness of comparable devices"

Clinical Evaluation
General Principles

- What is Clinical Evaluation?

- A **scientifically sound ongoing** procedure:
  - o to collect, assess and analyse **clinical data** (pre and post-market) on a medical device and comparable device
  - o evaluate the safety, clinical performance and or effectiveness
  - o when used as intended by the mf

Clinical evaluation and life cycle of medical device



Risk Management
hazards, clinical risks, risk mitigation, significance, benefit risk profile

Clinical Evaluation
clinical data and evidence in CER

PMS
clinical experience, safety reports, published lit, registry, PMCF

Labeling (IFU, label)
Impacted by all processes

Clinical Evaluation History

IMDRF MDCE WG/N56FINAL:2019 (formerly GHTF/SG5/N2R8:2007

IMDRF International Medical Device Regulators Forum

FINAL DOCUMENT

International Medical Device Regulators Forum

Title: Clinical Evaluation

Authoring Group: Medical Device Clinical Evaluation Working Group

Date: 10 October 2019

Elena M. Astapenko, IMDRF Chair

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- Global Harmonization Task Force (GHTF) Clinical Evaluation May 2007(GHTF/SG5/N2R8:2007)
- IMDRF Clinical Evaluation October 2019 (WG/N56FINAL:2019)
- Used globally and implemented globally
  - EU MEDDEV 2.7/1, Rev. 4, June 2016 Clinical Evaluation: A guide for manufacturers and Notified Bodies under Directives 93/42/EEC and 90/385/EEC

Clinical Evaluation
General Principles

- Sufficient clinical evidence to confirm compliance with EPs for safety and performance and "generally acknowledged state of the art" (IMDRF 5.1.1, 5.1.2, 5.1.8, 5.2; MDD Annex I, EP 1, 3, 6)
- Benefits and risks specified, acceptable
  - Known foreseeable risks minimized
- Claims related to safety, clinical performance, and effectiveness are supported

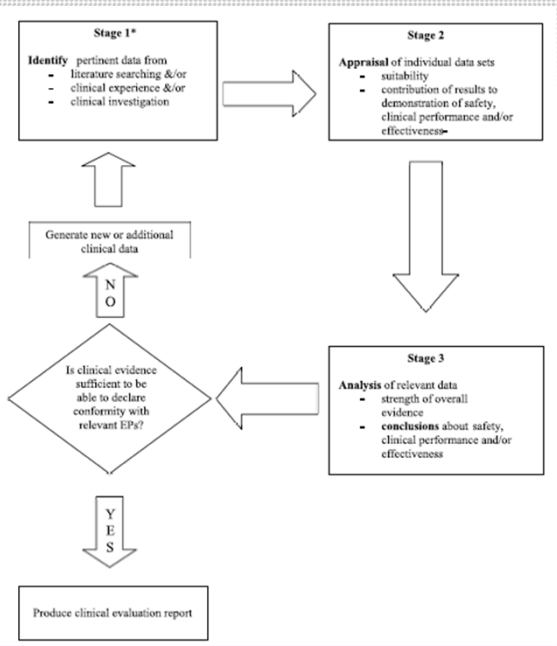
Clinical Evaluation

When is clinical evaluation undertaken and why is it important?

- Ongoing, throughout the life cycle of the medical device
- Clinical evaluation for device development:
  - Define safety and performance requirements
  - Identify data needed to be generated for regulatory purposes
  - Determine if clinical investigation is needed
- Clinical evaluation for regulatory submission:
  - Sufficient clinical evidence to support the EPs and safety and performance
  - Identify any aspects for PMS and the need for post market studies

Process

Process



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Clinical Evaluation

CER Template Appendix G

1. General details

2. Description of the medical device and its intended application

3. Intended therapeutic and/or diagnostic indications and claims

4. Context of the evaluation and choice of clinical data types
    - 4.1 type of evaluation
    - 4.2 demonstration of equivalence
    - 4.3 clinical data generated and held by manufacturer
    - 4.4 clinical data from literature
    - 4.5 summary and appraisal

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Clinical Evaluation

CER Template Appendix G

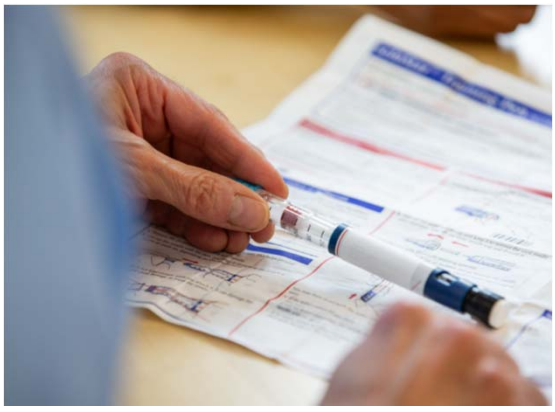
5. Summary of the clinical data and appraisal

6. Data analysis
    - 6.1 performance
    - 6.2 safety
    - 6.3 product labelling

7. Conclusion

Clinical Evaluation

How detailed should it be?



"*Many devices are developed or modified by incremental innovation, so they are not completely novel. Thus, it is often possible to draw on the clinical experience and literature reports of the safety, clinical performance and/or effectiveness of comparable devices to establish the clinical evidence, thereby reducing the need for clinical data generated through clinical investigation of the medical device in question. Similarly, it may be possible to use compliance with recognized standards to satisfy the clinical evidence requirements for devices based on technologies with well-established safety, clinical performance and/or effectiveness characteristics*."

ansm
Agence nationale de sécurité du médicament et des produits de santé

Fiche des degrés de nouveauté d'un dispositif médical

Degrees of novelty card for a medical device

Degré de nouveauté
Degree of novelty

Degré de nouveauté *Degree of novelty*	Type de nouveauté *Type of novelty*	Nouveauté à dominante *Innovation where the dominant is :* Technologique *Technological*		Clinique *Clinical*
5	**Innovation majeure** *Major innovation*	Rupture technologique *Breaking technology*	et *and*	Impact clinique fort *Strong clinical impact*
4	**Innovation** (dispositif innovant) *(innovative device)*	Rupture technologique *Breaking technology*	ou *or*	Impact clinique fort *Strong clinical impact*
3	**Nouveauté substantielle** *Substantial novelty*	Incrémentation technique *Incremental technology*	et *and*	Impact clinique modéré *Moderate clinical impact*
2	**Nouveauté modérée** *Modarate novelty*	Incrémentation technique *Incremental technology*	ou *or*	Impact clinique modéré *Moderate clinical impact*
1	**Nouveauté inexistante ou mineure** *Lacking or minor novelty*	Technologie connue *Known technology*	et	Impact clinique inchangé *Unchanged clinical impact*

ANSM 05/2012,

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Clinical Evaluation

Who should perform the clinical evaluation?

- Suitably qualified individual or team ("evaluator(s)"):
  - device technology and application
  - research methodology (clinical investigation design and biostatistics)
  - diagnosis management of clinical conditions intended to be treated or diagnosed

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Clinical Evaluation
Scope (Stage 0)

- Identification of EP required support from clinical data
- Define the scope
  - Description of the device
  - Particular design, indication, or population issues to consider
  - Information needed to support comparable devices
  - Risk management documentation – clinical risks to be addressed
  - Current knowledge/state of the art in the field

Clinical Evaluation
Identification of Pertinent Data (Stage 1)

Three category of sources of data:

Data generated through literature searching of the device in question (or comparable device) (6.1);

Data generated through clinical experience of the device in question (or comparable device) (6.2);

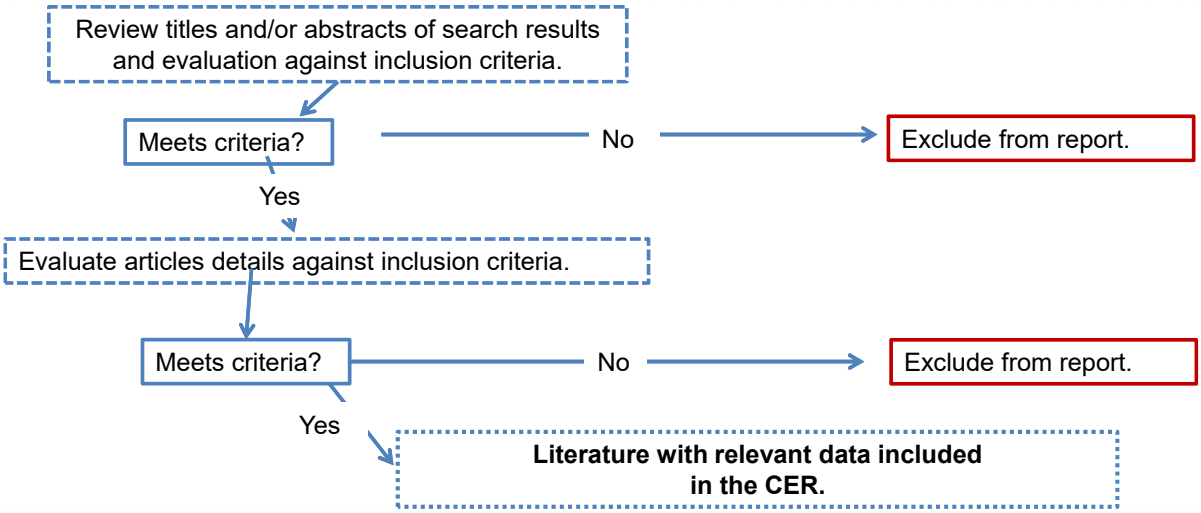
Data from clinical investigation(s) of the device in question (or comparable device) (6.3).

Clinical Evaluation

Data generated through literature searching

- Sources of data
- Scientific literature databases
  - Scientific databases: Pubmed/Medline, EMBASE
  - Systematic review databases: Cochrane Collection, NICE (UK National Institute for Clinical Excellence)
  - Clinical trial registers: CENTRAL, Clinical Trials.gov (USA)
  - Vigilance databases: MAUDE (US FDA), TPLC (US FDA), IRIS
- Internet searches
- Non-published data: e.g., implant registries, data presented at congress
- Citations referenced in retrieved papers “hand searching”

Citation Assessment Flowchart



Clinical Evaluation

Identification of Pertinent Data (Stage 1)

Examples of data generated through clinical experience

Examples

- Complaints
- Sales figures
- Individual customer feedback
- Customer questionnaires
- Customer focus groups
- Post market surveillance reports
- Internal registries
- FSCAs
- Use as a custom device
- Analysis of explanted devices
- Compassionate use
- Verification and Validation Reports (compliance to certain standards)

Clinical Evaluation

Identification of Pertinent Data (Stage 1)

Examples of data from clinical investigations

Data from clinical studies, documentation requirements:

- Clinical investigation protocol (and any amendments)
- Case report forms
- Ethics committee approvals
- Regulatory approvals (e.g., MHRA)
- Signed and dated clinical investigation report
- Analysis confirming applicability
- Gap analysis if not conducted to EN ISO 14155

Clinical Evaluation

Data generated through literature searching

"*For some medical devices, clinical data generated through literature searching will represent the greater part (if not all) of the clinical evidence. Thus, when conducting a literature review reasonable efforts should be made to conduct a comprehensive search*."

Clinical Evaluation

Comparable table, example

CRITERIA	Subject device Differences	Comparable device
Intended Use		
Indications for use	Clinical purpose/application. Therapeutic/diagnostic?	
Patient population	Adult? Pediatric?	
Technical aspects		
Conditions of use	Design features, mode operation	
Design/Specs	Technical characteristics	
Biological aspects		
Sterilization	Sterile? End user to sterilize?	

Clinical Evaluation
Appraisal of Pertinent Data (Stage 2)

- Appraisal process
- Identify information contained in each document
- Evaluate the methodological quality of work done by the authors and from that, the scientific validity of the information
- Determine the relevance of the information to the clinical evaluation
- Systematically weight the contribution of each data set to the clinical evaluation
- Criteria to determine:
  - methodological quality and scientific validity of each data set (9.3.1)
  - the relevance of the information to the device and intended purpose (9.3.2)
  - the contribution of each data set to the clinical evaluation (9.3.3)
- Appraisal can be qualitative or quantitative

Appraisal of Pertinent Data (Stage 2)
Weight contribution

- No single well-established method
- Justified basis current knowledge/state of the art
- Qualitative and quantitative
  - qualitative for well established and low risk
  - quantitative for vigilance
- RCT
- Appendix F

Weight Contribution Appendix F

A Possible Method of Appraisal, Suitability

Sutability Criteria	Description		Grading System
Appropriate device	Were the data generated from the device in question?	D1 D2 D3	Actual device Equivalent device Other device
Appropriate device application	Was the device used for the same intended use (e.g., methods of deployment, application, etc.)?	A1 A2 A3	Same use Minor deviation Major deviation
Appropriate patient group	Where the data generated from a patient group that is representative of the intended treatment population e.g., age, sex, etc.) and clinical condition (i.e., disease, including state and severity)?	P1 P2 P3	Applicable Limited Different population
Acceptable report/data collation	Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?	R1 R2 R3	High quality Minor deficiencies Insufficient information

Weight Contribution Appendix F

A Possible Method of Appraisal, Suitability

Data Contribution Criteria	Description		Grading System
Data source type	Was the design of the study appropriate?	T1 T2	Yes No
Outcome measures	Do the outcome measures reported reflect the intended performance of the device?	O1 O2	Yes No
Follow up	Is the duration of follow-up long enough to assess whether duration of treatment effects and identify complications?	F1 F2	Yes No
Statistical significance	Has a statistical analysis of the data been provided and is it appropriate?	S1 S2	Yes No
Clinical significance	Was the magnitude of the treatment effect observed clinically significant?	C1 C2	Yes No

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Weight Contribution, Oxford Centre for Evidence-based Medicine-Levels of Evidence (March 2009)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR" validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR" with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval"ǂ)	Individual inception cohort study with > 80% follow-up; CDR" validated in a single population	Validating** cohort study with good" " " reference standards; or CDR" tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts" "	All or none case-series	Absolute better-value or worse-value analyses " " " "
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR" or validated on split-sample§§§ only	Exploratory** cohort study with good" " " reference standards; CDR" after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

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Example New Appraisal Values Safety and Performance of the Device

Appraisal Criteria	Description	Grading System	
Study Design	Consider the type of study and the degree to which the design is defined and reported	D1	RCT
		D2	Prospective on randomized
		D3	Retrospective defined protocol
		D4	Not reported
Patient Population	Adequacy of inclusion /exclusion criteria and stratification of patients with respect to age , medical indication, severity of the condition, gender, other prognostic factors	P1	High
		P2	Low
		P3	Not reported
Study Endpoints	Adequacy of the study endpoints	E1	High
		E2	Low
		E3	Not reported
Length of Follow Up	Adequacy of follow up for safety and performance	F1	Long Term
		F2	Short/Medium Term
		F3	Not reported
Losses to Follow Up	Consider impact of losses to follow up on the integrity of the study	L1	No/Low impact
		L2	some impact
		L3	High Impact
Performance Outcomes	Do the performance outcome measures reflect the state of the art	PO1	High
		PO2	Low
		PO3	Not reported
Safety Outcomes	Do the Safety outcome measures reflect the state of the art	SO1	High
		SO2	Low
		SO3	Not reported
Statistical Methods	Consider adequacy of statistical methods, including sample size	S1	High
		S2	Low
		S3	Not reported

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Example Data Contribution Appraisal Table
Safety and Performance of the device

Ref.	Author	Data Source Type?	Outcome Measures?	Appropriate Follow-Up?	Statistically Significant?	Clinically Significant?	Suitable for :		
							Performance	Safety	State of the art
	[Name (YYYY)]								

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Clinical Evaluation
Analysis of the Data (Stage 3)

Data on the device/comparable devices

- Summary of each data set included:
  - Table is recommended
  - Population, number of patients, treatment details
  - Follow up evaluations
  - Key performance and safety results
  - Conclusions

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Clinical Evaluation

Analysis of the Data (Stage 3)

Requirement on safety (IMDRF 5.1.1):

- Special design features which pose a risk
- Have the risks identified in the risk management documentation and the literature (including vigilance databases) been addressed?
- Have all hazards been identified?
- Is training required to use the device?
- Consistency between the state of the art , RM docs, and IFU

Example Summary Clinical Data Table

Clinical Data	Contribution		
	Safety	Performance	State of the Art
Published clinical data			
1.			
2.			
Clinical data Generated and Held by Manufacturer			
Pre-Clinical Studies			
1.			
2.			
Clinical Investigations			
1.			
Clinical Experience – History			
Clinical Experience – Performance			
Clinical Experience – Safety			

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Requirement on safety Mitigation of Clinical Risks

Clinical Risks	Mitigation Plan		
	Identification (Risk#, CAPA#)	Mitigation Plan Description	Status
From Literature			
From Post-Market Surveillance			
From Clinical Data Generated and Held by [Manufacturer]			

Clinical Evaluation

Analysis of the Data (Stage 3)

Requirement on acceptable benefit/risk profile (IMDRF 5.1.2, 5.1.8)

- Summary of the total experience with the device
- Estimated numbers and characteristics of patients exposed
- Duration of follow-up
- Nature, extent/severity, probability/frequency, duration of benefits to the patients and of undesirable side-effects and other risks
- Is the risk/benefit profile compatible with a high level of protection of health and safety?

Requirement Acceptable Benefit/Risk Comparison Table State of the Art/Current Knowledge

Treatment	Advantages / Benefits	Disadvantages / Risks	Citation
Device Indications 1/2/3	- - -	- - -	[]
Alternative Treatment Option 1 Indications 1/2/3	- - -	- - -	[]
Alternative Treatment Option 2 Indications 1/2/3	- - -	- - -	[]
Alternative Treatment Option 3 Indications 1/2/3	- - -	- - -	[]

Clinical Evaluation

Analysis of the Data (Stage 3)

Requirement on performance (IMDRF 5.1.1)

- Description of clinical performance
- For each intended performance, extent to which evaluation of benefits is possible based on available data,
- Limitations of the data, description of gaps, uncertainties or unanswered questions, and assumptions
- Whether available data allows adequate evaluation of performance
- Whether there is sufficient clinical evidence for every intended performance

Clinical Evaluation
Analysis of the Data (Stage 3)

Requirement on acceptability of side-effects (IMDRF 5.1.8)

- Whether the data available is of sufficient amount and quality for the detection of undesirable side-effects and their frequency
- Limitations of the data, description of gaps, uncertainties or unanswered questions, and assumptions.
- Whether the undesirable side-effects are acceptable and corresponding justifications

Clinical Evaluation
Analysis of the Data (Stage 3)

Conclusions

- Clear statement concerning compliance to EP
- Acceptability of the benefit/risk profile according to current knowledge/the state
- Adequacy of the information materials supplied by the manufacturer
- Suitability of the device, including its IFU, for the intended users
- Adequacy of claims
- Consistency between the clinical data, the IFU, and RM docs
- Consistency between these docs and the state of the art
- Whether any residual risks, uncertainties, unanswered questions are acceptable for CE marking
- Follow up during PMS/post market studies

Clinical Evaluation
CER (Stage 4)

General Points:

- Sufficiently detailed to be read by an independent party
- Cross references to supporting documents
- It should be clear which statements are substantiated by which data, and which reflect the conclusions or opinions of the evaluators
- Report should outline the different stage of the evaluation

Clinical Evaluation
Concluding remarks

- On-going iterative methodical process
- Clinical evidence to confirm compliance with EPs for safety and performance and “generally acknowledged state of the art”
- Support claims related to safety, clinical performance and effectiveness
- Data sources (device or comparable device): literature, clinical experience, clinical investigations
- Consistency in the regulatory documents
  - RM, labelling, PMS, and Clinical Evaluation Report
- Documented in Clinical Evaluation Report, revised and reviewed on-going

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Regulatory Science Virtual Symposium

Principles of Global Clinical Research for Medical Devices

Wrap-Up!

Eunjoo Pacifici, PharmD, PhD
Chair and Associate Professor, Regulatory and Quality Sciences
Associate Director, DK Kim International Center for Regulatory Science

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