Ecker - Labek - Mittermayr - Raffeiner - Ring - Schwartz

Clinical Evaluation and Investigation of Medical Devices under the new EU-Regulation

Acknowledgements
We want to thank Cornelia Hoflehner for her continuous support on this project, for her outstanding engagement and for her great patience during the creation of this book.

Wolfgang Ecker
Thanks his former national, EU/EEA and GHTF colleagues for interesting discussions and especially his wife Sigrid for continuous support.

Gerold Labek
Many thanks to Wolfgang Ecker and numerous colleagues from regulatory bodies in Europe and IMDRF for their critical review on concepts and ideas to realize new requirements in real world processes. I also would like to thank colleagues from more than 40 universities and research centers in Europe, Ankara and Jerusalem for their support in projects to study limitations in the value of clinical data and procedures to assure safety and performance of medical devices for patients.

Tarquin Mittermayr
Many thanks to the ‘Film Team’ Sandra Meinschad and Michael Ring for adding audiovisual sparkle to my chapter through their professional conversion of text passages and graphics into comprehensible words and appealing images. Additionally, I would like to thank everyone who provided me with encouragement, food and patience during the writing process.

Brigitte Raffeiner
My first thanks go to Mag. Andreas Raffeiner GmbH who made it possible for me to dedicate parts of my working time and my knowledge to this book. Furthermore, I would

like to thank my family and friends, who have been very patient with me while writing the text passages of this book.

Michael Ring
I want to thank Sandra E. Mae for her awesome work regarding the creation, voice-over and cutting of the tutorial videos.

Bernhard Schwartz
I want to thank Michael Ring and the other authors for giving me the opportunity to provide a brief insight into biostatics and statistical planning of clinical trials.

Hon (FH) Prof. Dr. Wolfgang Ecker MD, graduated at the Medical Faculty of the University of Vienna, has accomplished his medical training as GP in various Viennese hospitals. He has served the Austrian Health Ministry and the EU Medical Device Sector for 30 years. He has been member of various expert groups at EU level, i.a. as Chair of the EU Working Group on Clinical Investigation and Evaluation (CIE) and as an EU representative in GHTF Study Group 5 on Clinical Evidence. As a member of the EU Council Working Group on Medical Devices, he has helped shaping the new EU Regulations on Medical Devices and IVDs. He is giving lectures and training seminars on these new Regulations at various Universities of Applied Sciences in Austria and at Health Technology Clusters.

Ass. Prof. Dr Gerold Labek MD, graduated at the medical faculty of Vienna University. He has accomplished training for General Practitioner and senior consultant for orthopedic surgery at AKH Linz (now Kepler University Clinic Linz). He conducted research focused on the topics of registries/real world evidence and quality of published research for almost 20 years and received habilitation at Innsbruck Medical University on research methodology.

He was been working for the Notified Body TÜV SÜD as Director for Clinical Market Surveillance and is active now as clinical expert for several Notified Bodies.

Tarquin Mittermayr BA(Hons) MA, is an Information Specialist at the Austrian Institute for Health Technology Assessment (AIHTA), where he is responsible for the institute's information management including the systematic searching for scientific literature. He studied History, Archive and Museum Studies as well as German, European Studies and Bookbinding. He worked as an assistant librarian at the monastery of St. Florian, as an Information Assistant at Roehampton University and St. George's Hospital Medical School (University of London), and more recently as an archivist at the Konrad Lorenz Institute for Evolution & Cognition Research.

Brigitte Raffeiner PMSc, is CEO of the Competence Center for Medical Devices GmbH (CCMD). Her personal focal points in the company are corporate management, project management, monitoring and data management. She can look back on many years of experience in the handling of clinical studies. Together with her partners, she supports companies in successfully bringing their products to market.

DI (FH) Dr. Michael Ring, is co-founder and one of the managing directors of R'n'B Consulting GmbH and co-founder and consultant at the Competence Center for Medical Devices GmbH (CCMD). Together with his business partners and cooperation partners, he supports companies in the medical technology industry in the compliant implementation of the process of the clinical evaluation, including the conduct of clinical investigations and systematic literature searches.

In addition, Michael worked from 2014 to 2019 as a study coordinator at the newly established Kepler University Hospital in Linz. His responsibilities included the coordination of sponsored studies and academic research.

Dr. Bernhard Schwartz BSc MSc, is a researcher at the University of Vienna and at the University for Applied Sciences for Health Professions Upper Austria as well as a co-founder of Competence Center for Medical Devices GmbH (CCMD). As scientific member and biometrician at an institutional ethics board and laureate of an Austrian State Price for science (Award of Excellence), he - in partnership with the other CCMD members – supports customers in the

pharmacological and medical technology industry in planning, execution and statistical analysis of clinical trials. In addition, Bernhard regularly conducts systematic reviews, clinical evaluations and mini health technology assessments (mini HTAs). Based on his former experience in the field of toxicology (Seibersdorf Laboratories) and medical devices (University for Applied Sciences Upper Austria), he has a perfect background for solving clinical and technical problems.

Foreword

‘I first met Wolfgang in 2015, having moved from working as a busy junior doctor in an Irish hospital to working as a medical officer for medical devices for my national Authority.

In my second week on the job, I was asked to attend a meeting in Brussels to discuss what became Annex VII of the Medical Device Regulation. I still remember being introduced to Wolfgang and I was immediately struck by his kind and enthusiastic manner. Wolfgang was a key figure in representing the importance of clinical evidence as part of the European Council Working Party negotiations for the Medical Device Regulation. At the Clinical Investigation and Evaluation Working Group, Wolfgang also worked very hard to ensure progress the last revision of the guidance for clinical evaluation (MEDDEV 2.7/1 revision 4), in addition to a range of other technical achievements.

In Europe, you learn very quickly that achieving progress requires teamwork, consultation and effective communication. This textbook represents a thorough and detailed guidance, with many practical and useful elements to help medical device developers to meet the requirements of the new Regulation.

When I speak about medical device regulations, I often find myself explaining the differences between medical devices and medicinal products, in terms of the numbers of products, the decision makers for market access, the legal standard for clinical evidence, but also the differences of profiles of drug and device developers. Medical devices are often developed in smaller institutions, whether ‘spin-out’ companies or small and medium sized enterprises. As such, a thorough and practical textbook explaining the

requirements and providing practical solutions is an important addition to the available knowledge and I congratulate Wolfgang and the fellow authors for their achievement.’

Dr. Tom Melvin
Co-Chair, Clinical Investigation and Evaluation Working Group

Table of Contents

List of Abbreviations

Abbreviation	Definition, Explanation, Remarks
acc.	According to
AIMDD	Active Implantable Medical Device Directive 90/385/EEC
App.	Appendix (used in MEDDEV 2.7.1. rev. 4)
Art.	Article (of MDR)
Basic UDI DI	Basic UDI Device Identifier
B/R	Benefit/Risk
B/R-R	Benefit/Risk-Ratio
CA	Competend Authority
CDRH	Center for Devices and Radiological Health (of FDA)
CEAR	Clinical Evaluation Assessment Report
CEN	Comitee Europeene de Normalisation (European Standardisation Committee)
CENELEC	European Committee for Electrotechnical Standardization
CER	Clinical Evaluation Report
CIE	Working Group for Clinical Investigation and Evaluation of the EU MDEG
CIP	Clinical Investigation Plan
COM	Commission of the European Community
COMET	Core Outcome Measures in Effectiveness Trials (comet-initiative.org)
CRA	Clinical Research Associate / Monitor
CRF	Case Report Form
CRO	Clinical Research Organisation

CS	Common Specification (Art. 9 of MDR)
CV	Curriculum Vitae
DD	Device Deficiency
DoI	Declaration of Interest
DSG	Device Specific Guidance
EbM	Evidence based Medicine
EC	Ethics Committee
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EUDAMED	European Database for Medical Devices
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EUnetHTA	European network for health technology assessment
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GHTF	Global Harmonisation Task Force, now superseded by IMDRF
GMDN	Global Medical Device Nomenclatura
GSPR	General Safety and Performance Requirements, see Annex I of MDR
HN	Harmonised Norm – EU Harmonised Standard with presumptions of conformity in their Annexes Z for specific Directives/Regulations of EU
HTA	Health Technology Assessment
IB	Investigators Brochure
ICH	International Council for Harmonisation of

	Technical Requirements for Pharmaceuticals for Human Use
IEC	International Electrotechnical Commission
IMDRF	International Medical Device Regulatory Forum, Successor of GHTF
IP	Investigational Product
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISF	Investigator Site File
ISO	International Standardization Organization
IVD	In Vitro Diagnostic (Medical Device)
IVDR	IVD Regulation (EU) 2017/746
MDCG	Medical Device Coordination Committee
MDEG	Medical Device Expert Group of EU, now superseded by MDCG
MEDDEV	Medical Device Guideline of the EU COM, now superseded by MDCG-Guidance
MD	Medical Device
MDD	Medical Device Directive 93/42/EEC
MDR	Medical Device Regulation (EU) 2017/745
NB	Notified Body
NCBI	National Center for Biotechnology Information
PI	Principal Investigator
PICO	HTA structured search strategy with Population; Intervention; Control/Comparator; Outcome(s)
PLEG	Post Launch Evidence Generation; Concept

	in HTA for post market evidence generation
PMCF	Post-Market Clinical Follow-Up
PMS	Post Market Surveillance, see Chapter VII.1 and Annex III of MDR
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses
PSUR	Periodic Safety Update Report, see Art. 86 of MDR
rev.	Revision (MEDDEV 2.7.1. rev. 4)
RMS	Risk Management System
RWD	Real World Data – Concept of IMDRF for post market evidence generation
RWE	Real World Evidence
SAE	Serious Adverse Event
SaMD	Software as a Medical Device (IMDRF concept)
SMF	Study Master File
SOP	Standard Operation Procedures
SRN	Single Registration Number (of manufacturer, authorized representative or importer) in EUDAMED
SSCP	Summary of Safety and Clinical Performance, see Art. 32 of MDR
TD	Technical Documentation
TPLC	Total Product Life Cycle – Concept of IDEAL D Initiative
UDI	Unique Device Identifier
WHO	World Health Organization

WHO ICTRP	World Health Organization International Clinical Trials Registry Platform

Symbol meanings

Symbol for relevant hints:

Hint

Symbol for MDR citation:

Citation

Symbol for Guidance (MEDDEV, MDCG, GHTF/IMDRF etc) citation:

Citation

The QR Codes shown in this book can be captured by a QR Code Scanner, which allows a forwarding to the website where the videos and supporting documents are provided.

Further reference material and updates (e.g. references to new MDCG Guidelines ...) can be found under the following link:
https://www.rnb-consulting.at/doku/doku.php/en/referenzen/start